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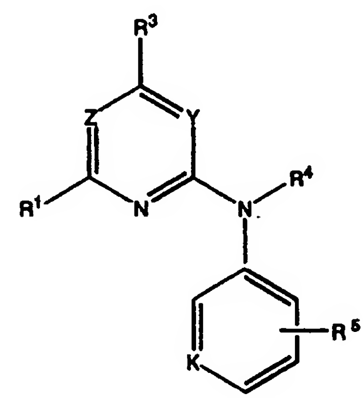
(54) Title: ARYL-AND ARYLAMINO-SUBSTITUTED HETEROCYCLES AS CORTICOTROPIN RELEASING HORMONE ANTAGONISTS

(57) Abstract

Corticotropin releasing factor (CRF) antagonists of formula (I), and their use in treating psychiatric disorders and neurological diseases, anxiety-related disorders, post-traumatic stress disorder, supranuclear palsy and feeding disorders as well as treatment of immunological, cardiovascular or heart-related diseases and colonic hypersensitivity associated with psychopathological disturbance and stress in mammals.



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TITLE

ARYL- AND ARYLAMINO- SUBSTITUTED HETEROCYCLES AS CORTICOTROPIN RELEASING HORMONE ANTAGONISTS

FIELD OF THE INVENTION

The present invention relates to novel compounds, compositions, and methods for the treatment of psychiatric disorders and neurological diseases, including major depression, anxiety-related disorders, post-traumatic stress disorder, supranuclear palsy and feeding disorders, as well as treatment of immunological, cardiovascular or heart-related diseases and colonic hypersensitivity associated with psychopathological disturbance and stress. In particular, the present invention relates to certain arylamino-substituted pyrimidines and triazines or certain aryl-substituted azolopyridines and pyrimidines, pharmaceutical compositions containing such compounds and their use in treating psychiatric disorders, neurological diseases, immunological, cardiovascular or heart-related diseases and colonic hypersensitivity associated with psychopathological disturbance and stress

BACKGROUND OF THE INVENTION

Corticotropin releasing factor (herein referred to as CRF), a 41 amino acid peptide, is the primary physiological regulator of proopiomelanocortin(POMC) - derived peptide secretion from the anterior pituitary gland [J. Rivier et al., *Proc. Nat. Acad. Sci. (USA)* 80:4851 (**1983**); W. Vale et al., *Science* 213:1394 (**1981**)]. In addition to its endocrine role at the pituitary gland, immunohistochemical localization of CRF has demonstrated that the hormone has a broad extrahypothalamic distribution in the central nervous system and produces a wide spectrum of autonomic,

electrophysiological and behavioral effects consistent with a neurotransmitter or neuromodulator role in brain [W. Vale et al., *Rec. Prog. Horm. Res.* 39:245 (**1983**); G.F. Koob, *Persp. Behav. Med.* 2:39 (**1985**); E.B. De Souza et al., *J. Neurosci.* 5:3189 (**1985**)]. There is also evidence that CRF plays a significant role in integrating the response of the immune system to physiological, psychological, and immunological stressors [J.E. Blalock, *Physiological Reviews* 69:1 (**1989**); J.E. Morley, *Life Sci.* 41:527 (**1987**)].

Clinical data provide evidence that CRF has a role in psychiatric disorders and neurological diseases including depression, anxiety-related disorders and feeding disorders. A role for CRF has also been postulated in the etiology and pathophysiology of Alzheimer's disease, Parkinson's disease, Huntington's disease, progressive supranuclear palsy and amyotrophic lateral sclerosis as they relate to the dysfunction of CRF neurons in the central nervous system [for review see E.B. De Souza, *Hosp. Practice* 23:59 (**1988**)].

In affective disorder, or major depression, the concentration of CRF is significantly increased in the cerebral spinal fluid (CSF) of drug-free individuals [C.B. Nemeroff et al., *Science* 226:1342 (**1984**); C.M. Banki et al., *Am. J. Psychiatry* 144:873 (**1987**); R.D. France et al., *Biol. Psychiatry* 28:86 (**1988**); M. Arato et al., *Biol Psychiatry* 25:355 (**1989**)]. Furthermore, the density of CRF receptors is significantly decreased in the frontal cortex of suicide victims, consistent with a hypersecretion of CRF [C.B. Nemeroff et al., *Arch. Gen. Psychiatry* 45:577 (**1988**)]. In addition, there is a blunted adrenocorticotropin (ACTH) response to CRF (i.v. administered) observed in depressed patients [P.W. Gold et al., *Am J. Psychiatry* 141:619 (**1984**); F. Holsboer et al., *Psychoneuroendocrinology* 9:147

(**1984**); P.W. Gold et al., *New Eng. J. Med.* 314:1129 (**1986**)]. Preclinical studies in rats and non-human primates provide additional support for the hypothesis that hypersecretion of CRF may be involved in the symptoms seen in human depression [R.M. Sapolsky, *Arch. Gen. Psychiatry* 46:1047 (**1989**)]. There is preliminary evidence that tricyclic antidepressants can alter CRF levels and thus modulate the numbers of CRF receptors in brain [Grigoriadis et al., *Neuropsychopharmacology* 2:53 (**1989**)].

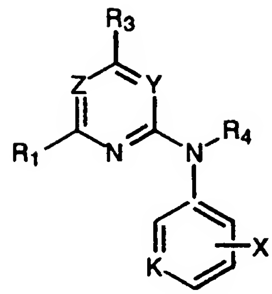
There has also been a role postulated for CRF in the etiology of anxiety-related disorders. CRF produces anxiogenic effects in animals and interactions between benzodiazepine / non-benzodiazepine anxiolytics and CRF have been demonstrated in a variety of behavioral anxiety models [D.R. Britton et al., *Life Sci.* 31:363 (**1982**); C.W. Berridge and A.J. Dunn *Regul. Peptides* 16:83 (**1986**)]. Preliminary studies using the putative CRF receptor antagonist a-helical ovine CRF (9-41) in a variety of behavioral paradigms demonstrate that the antagonist produces "anxiolytic-like" effects that are qualitatively similar to the benzodiazepines [C.W. Berridge and A.J. Dunn *Horm. Behav.* 21:393 (**1987**), *Brain Research Reviews* 15:71 (**1990**)]. Neurochemical, endocrine and receptor binding studies have all demonstrated interactions between CRF and benzodiazepine anxiolytics providing further evidence for the involvement of CRF in these disorders. Chlordiazepoxide attenuates the "anxiogenic" effects of CRF in both the conflict test [K.T. Britton et al., *Psychopharmacology* 86:170 (**1985**); K.T. Britton et al., *Psychopharmacology* 94:306 (**1988**)] and in the acoustic startle test [N.R. Swerdlow et al., *Psychopharmacology* 88:147 (**1986**)] in rats. The benzodiazepine receptor antagonist (Ro15-1788), which was without behavioral activity alone in the operant

conflict test, reversed the effects of CRF in a dose-dependent manner while the benzodiazepine inverse agonist (FG7142) enhanced the actions of CRF [K.T. Britton et al., *Psychopharmacology* 94:306 (**1988**)].

It has been further postulated that CRF has a role in immunological, cardiovascular or heart-related diseases such as hypertension, tachycardia and congestive heart failure, stroke, osteoporosis, premature birth, psychosocial dwarfism, stress-induced fever, ulcer, diarrhea, post-operative ileus and colonic hypersensitivity associated with psychopathological disturbance and stress.

The mechanisms and sites of action through which the standard anxiolytics and antidepressants produce their therapeutic effects remain to be elucidated. It has been hypothesized however, that they are involved in the suppression of the CRF hypersecretion that is observed in these disorders. Of particular interest is that preliminary studies examining the effects of a CRF receptor antagonist (a-helical CRF_{9-41}) in a variety of behavioral paradigms have demonstrated that the CRF antagonist produces "anxiolytic-like" effects qualitatively similar to the benzodiazepines [for review see G.F. Koob and K.T. Britton, In: *Corticotropin-Releasing Factor: Basic and Clinical Studies of a Neuropeptide*, E.B. De Souza and C.B. Nemeroff eds., CRC Press p221 (1990)].

Aldrich et al. (DuPont Merck) PCT Application US94/11050 describes a broad class of CRF antagonist compounds, including compounds which can be represented by the formula:



wherein R^3 can be phenyl, biphenyl, napthyl, pyridinyl, 2-methyl-3-pyridinyl, 4-methyl-3-pyridinyl, or pyrimidinyl and R1, R2, R4, K and X can have some of the same meanings as in this invention. The compounds of this invention do not include unsubstituted phenyl, biphenyl, napthyl, pyridinyl, or pyrimidinyl or 2-methyl-3-pyridinyl or 4-methyl-3-pyridinyl at the R^3 position.

Other compounds reported to have activity as corticotropin releasing factors are disclosed in WO 94/13676 and WO 94/13643.

SUMMARY OF THE INVENTION

In accordance with one aspect, the present invention provides novel compounds which bind to corticotropin releasing factor receptors, thereby altering the anxiogenic effects of CRF secretion. The compounds of the present invention are useful for the treatment of psychiatric disorders and neurological diseases, anxiety-related disorders, post-traumatic stress disorder, supranuclear palsy and feeding disorders as well as treatment of immunological, cardiovascular or heart-related diseases and colonic hypersensitivity associated with psychopathological disturbance and stress in mammals.

According to another aspect, the present invention provides novel compounds of formula (I) (described below) which are useful as antagonists of the corticotropin releasing factor. The compounds of the present invention exhibit activity as corticotropin releasing factor antagonists and appear to suppress CRF hypersecretion. The present invention also includes pharmaceutical compositions containing such compounds of formula (I), and methods of using such compounds for the suppression of CRF hypersecretion, and/or for the treatment of anxiogenic disorders.

According to yet another aspect, the present invention provides novel compounds, pharmaceutical compositions and methods which may be used in the treatment of affective disorder, anxiety, depression, irritable bowel syndrome, post-traumatic stress disorder, supranuclear palsy, immune suppression, Alzheimer's disease, gastrointestinal disease, anorexia nervosa or other feeding disorder, drug or alcohol withdrawal symptoms, drug addiction, inflammatory disorder, fertility problems, disorders, the treatment of which can be effected or facilitated by antagonizing CRF, including but not limited to disorders induced or facilitated by CRF, or a disorder selected from inflammatory disorders such as rheumatoid arthritis and osteoarthritis, pain, asthma, psoriasis and allergies; generalized anxiety disorder; panic, phobias, obsessive-compulsive disorder; post-traumatic stress disorder; sleep disorders induced by stress; pain perception such as fibromyalgia; mood disorders such as depression, including major depression, single episode depression, recurrent depression, child abuse induced depression, and postpartum depression; dysthemia; bipolar disorders; cyclothymia; fatigue syndrome; stress-induced

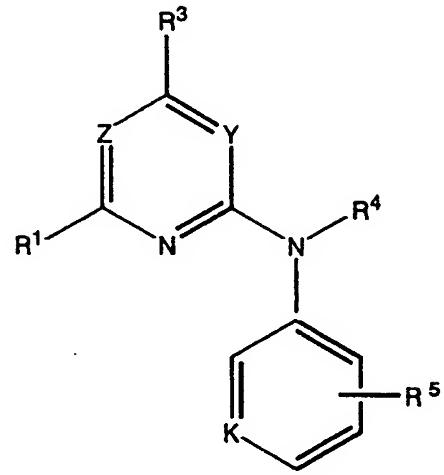
headache; cancer, human immunodeficiency virus (HIV) infections; neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and Huntington's disease; gastrointestinal diseases such as ulcers, irritable bowel syndrome, Crohn's disease, spastic colon, diarrhea, and post operative ilius and colonic hypersensitivity associated by psychopathological disturbances or stress; eating disorders such as anorexia and bulimia nervosa; hemorrhagic stress; stress-induced psychotic episodes; euthyroid sick syndrome; syndrome of inappropriate antidiarrhetic hormone (ADH); obesity; infertility; head traumas; spinal cord trauma; ischemic neuronal damage (e.g., cerebral ischemia such as cerebral hippocampal ischemia); excitotoxic neuronal damage; epilepsy; cardiovascular and hear related disorders including hypertension, tachycardia and congestive heart failure; stroke; immune dysfunctions including stress induced immune dysfunctions (e.g., stress induced fevers, porcine stress syndrome, bovine shipping fever, equine paroxysmal fibrillation, and dysfunctions induced by confinement in chickens, sheering stress in sheep or human-animal interaction related stress in dogs); muscular spasms; urinary incontinence; senile dementia of the Alzheimer's type; multiinfarct dementia; amyotrophic lateral sclerosis; chemical dependencies and addictions (e.g., dependencies on alcohol, cocaine, heroin, benzodiazepines, or other drugs); drug and alcohol withdrawal symptoms; osteoporosis; psychosocial dwarfism and hypoglycemia in mammals.

According to a still further aspect of the invention, the compounds provided by this invention (and especially labeled compounds of this invention) are also useful as standards and reagents in determining the

ability of a potential pharmaceutical to bind to the CRF receptor.

DETAILED DESCRIPTION OF THE INVENTION

[1] Thus, in a first embodiment, the present invention provides a method of treating affective disorder, anxiety, depression, headache, irritable bowel syndrome, post-traumatic stress disorder, supranuclear palsy, immune suppression, Alzheimer's disease, gastrointestinal diseases, anorexia nervosa or other feeding disorder, drug addiction, drug or alcohol withdrawal symptoms, inflammatory diseases, cardiovascular or heart-related diseases, fertility problems, human immunodeficiency virus infections, hemorrhagic stress, obesity, infertility, head and spinal cord traumas, epilepsy, stroke, ulcers, amyotrophic lateral sclerosis, hypoglycemia or a disorder the treatment of which can be effected or facilitated by antagonizing CRF, including but not limited to disorders induced or facilitated by CRF, in mammals, comprising: administering to the mammal a therapeutically effective amount of a compound of formula (I):



(I)

or a stereoisomer or pharmaceutically acceptable salt form thereof, wherein:

Y is CR^2 or N;

Z is CH or N;

K is CR^5 or N;

R^1 is C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, chloro, fluoro, cyano, or trifluoromethyl;

R^2 taken together with R^4 is -E-F-, where E and F are independently CR^9 and CR^{9a}; or R^2 taken together with R^4 is -A=D-, where A and D are each independently CH, CR^{10} or N; provided that -A=D- may not be -CH=N- or CR^{10}=N- oriented in such a way as to form a pyrazole ring, but may be -CH=N- or CR^{10}=N- oriented in such a way as to form an imidazole ring; or R^2 taken together with R^4 is -A-D- where A is NR^9 and D is C=O oriented in such a way as to form an imidazolone.

R^3 is phenyl substituted on 1-4 ring carbons with R^8, napthyl substituted on 1-4 ring carbons with R^8, pyridinyl substituted on 1-4 ring carbons with R^8, or pyrimidinyl substituted on 1-3 ring carbons with R^8;

R^4 is C_1-C_4 alkyl, allyl, or propargyl, where C_1-C_4 alkyl is optionally substituted with C_3-C_6 cycloalkyl, OH, $-OR^9$, $-S(O)_nR^9$ or $-CO_2R^9$;

R^5 represents 1-4 substituents on ring carbons each of which may be independently C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_6 cycloalkyl, C_4-C_{10} cycloalkylalkyl, halo, nitro,cyano, $-NR^6R^7$, $-OR^7$, $-COR^7$, $-C(O)NR^6R^7$, $-C(NOR^9)R^7$, or $-S(O)_nR^7$, where C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_6 cycloalkyl and C_4-C_{10} cycloalkylalkyl are optionally substituted with 1 to 3 substituents independently selected from halo, nitro, cyano, $-NR^6R^7$, $-OR^7$, $-COR^7$, $-C(O)NR^6R^7$, $-S(O)_nR^7$, and $-C(NOR^9)R^7$ and two R^5 moieties taken together may comprise $CR^9R^{9a}CR^9R^{9a}O$, $CR^9R^{9a}CR^9R^{9a}CR^9R^{9a}$, or $CR^9{=}CR^{9a}O$;

R^6 and R7 are independently at each occurrence H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, $-(CH_2)_m$-phenyl, or -$(CH_2)_m$-heteroaryl; all optionally substituted with 1-3 R^{11}'s.

R^8 is independently at each occurrence C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_4-C_{10} cycloalkylalkyl, phenyl, heteroaryl, halo, nitro,cyano, $-NR^6R^7$, $-OR^7$, $-COR^7$, $-CO_2R^7$, $-C(O)NR^6R^7$, $-OC(O)NR^6R^7$, $-NR^9C(O)NR^6R^7$, $-NR^6C(O)R^7$, $-C(NOR^9)R^7$, $-S(O)_nR^7$, $-NR^9SO_2R^7$, $-SO_2NR^6R^7$, and where C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl,

C_3-C_6 cycloalkyl, C_4-C_{10} cycloalkylalkyl, and phenyl are optionally substituted with 1 to 3 substituents independently selected from halo, nitro, cyano, $-NR^6R^7$, $-OR^7$, $-COR^7$, $-C(O)NR^6R^7$, $-S(O)_nR^7$, $-C(NOR^9)R^7$, $-NR^9SO_2R^7$, and $-SO_2NR^6R^7$; provided that when R^3 is pyridinyl, at least one R^8 is other than methyl; further provided that when R^3 is phenyl, at least one R^8 is other than unsubstituted phenyl;

R^9 and R^{9a} is H or C_1-C_4 alkyl;

R^{10} is C_1-C_4 alkyl, halo, nitro, cyano, $-NR^9R^{9a}$, $-OR^{12}$, or $-S(O)_nR^{12}$;

R^{11} is independently at each occurrence C_1-C_3 alkyl, halo, nitro, cyano, $-NR^9R^{9a}$, $-OR^9$ $-S(O)_nR^{12}$, $-COR^9$, $-CO_2R^9$, $-C(O)NR^9R^{9a}$, $-NR^9C(O)R^{9a}$, or $-C(NOR^9)R^{9a}$.

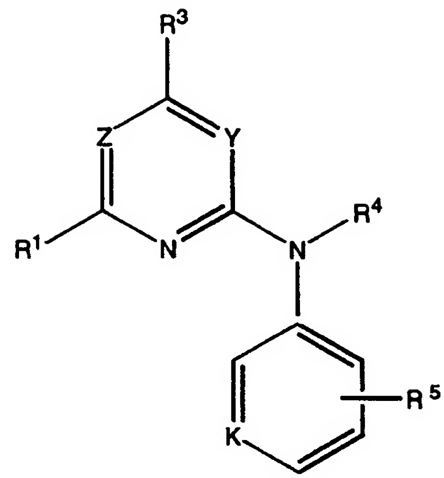
R^{12} is C_1-C_4 alkyl;

heteroaryl is pyridyl, pyrimidinyl, triazinyl, furanyl, quinolinyl, isoquinolinyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrrolyl, oxazolyl, benzofuranyl, benzothienyl, benzthiazolyl, isoxazolyl, pyrazolyl, triazolyl, tetrazolyl, indazolyl, 2,3-dihydrobenzofuranyl or 2,3-dihydrobenzothienyl;

n is independently at each occurrence 0, 1 or 2; and

m is independently at each occurrence 0-6.

[2] In a preferred embodiment, the present invention provides a novel compound of formula I:



(I)

or a stereoisomer or pharmaceutically acceptable salt form thereof, wherein:

Y is CR^2 or N;

Z is CH or N;

K is CR^5 or N;

R^1 is C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, chloro, fluoro, cyano, or trifluoromethyl;

R^2 taken together with R^4 is -E-F-, where E and F are independently CR^9 and CR^{9a}; or R^2 taken together with R^4 is -A=D-, where A and D are each independently CH, CR^{10} or N; provided that -A=D- may not be -CH=N- or CR^{10}=N- oriented in such a way as to form a pyrazole ring, but may be -CH=N- or CR^{10}=N- oriented in such a way as to form an imidazole ring; or R^2 taken together with R^4 is -A-D- where A is NR^9 and D is C=O oriented in such a way as to form an imidazolone.

R^3 is phenyl substituted on 1-4 ring carbons with R^8, napthyl substituted on 1-4 ring carbons with R^8, pyridinyl substituted on 1-4 ring carbons with R^8, or pyrimidinyl substituted on 1-3 ring carbons with R^8;

R^4 is C_1-C_4 alkyl, allyl, or propargyl, where C_1-C_4 alkyl is optionally substituted with C_3-C_6 cycloalkyl, OH, $-OR^9$, $-S(O)_nR^9$ or $-CO_2R^9$;

R^5 represents 1-4 substituents on ring carbons each of which may be independently C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_6 cycloalkyl, C_4-C_{10} cycloalkylalkyl, halo, nitro,cyano, $-NR^6R^7$, $-OR^7$, $-COR^7$, $-C(O)NR^6R^7$, $-C(NOR^9)R^7$, or $-S(O)_nR^7$, where C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_6 cycloalkyl and C_4-C_{10} cycloalkylalkyl are optionally substituted with 1 to 3 substituents independently selected from halo, nitro, cyano, $-NR^6R^7$, $-OR^7$, $-COR^7$, $-C(O)NR^6R^7$, $-S(O)_nR^7$, and $-C(NOR^9)R^7$ and two R^5 moieties taken together may comprise $CR^9R^{9a}CR^9R^{9a}O$, $CR^9R^{9a}CR^9R^{9a}CR^9R^{9a}$, or $CR^9{=}CR^{9a}O$;

R^6 and R7 are independently at each occurrence H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, $-(CH_2)_m$-phenyl, or $-(CH_2)_m$-heteroaryl; all optionally substituted with 1-3 R^{11}'s.

R^8 is independently at each occurrence C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_4-C_{10} cycloalkylalkyl, phenyl, heteroaryl, halo, nitro,cyano, $-NR^6R^7$, $-OR^7$, $-COR^7$, $-CO_2R^7$, $-C(O)NR^6R^7$, $-OC(O)NR^6R^7$, $-NR^9C(O)NR^6R^7$, $-NR^6C(O)R^7$, $-C(NOR^9)R^7$, $-S(O)_nR^7$, $-NR^9SO_2R^7$, $-SO_2NR^6R^7$, and where C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl,

C_3-C_6 cycloalkyl, C_4-C_{10} cycloalkylalkyl, and phenyl are optionally substituted with 1 to 3 substituents independently selected from halo, nitro, cyano, $-NR^6R^7$, $-OR^7$, $-COR^7$, $-C(O)NR^6R^7$, $-S(O)_nR^7$, $-C(NOR^9)R^7$, $-NR^9SO_2R^7$, and $-SO_2NR^6R^7$; provided that when R^3 is pyridinyl, at least one R^8 is other than methyl; further provided that when R^3 is phenyl, at least one R^8 is other than unsubstituted phenyl;

R^9 and R^{9a} is H or C_1-C_4 alkyl;

R^{10} is C_1-C_4 alkyl, halo, nitro, cyano, $-NR^9R^{9a}$, $-OR^{12}$, or $-S(O)_nR^{12}$;

R^{11} is independently at each occurrence C_1-C_3 alkyl, halo, nitro, cyano, $-NR^9R^{9a}$, $-OR^9$ $-S(O)_nR^{12}$, $-COR^9$, $-CO_2R^9$, $-C(O)NR^9R^{9a}$, $-NR^9C(O)R^{9a}$, or $-C(NOR^9)R^{9a}$.

R^{12} is C_1-C_4 alkyl;

heteroaryl is pyridyl, pyrimidinyl, triazinyl, furanyl, quinolinyl, isoquinolinyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrrolyl, oxazolyl, benzofuranyl, benzothienyl, benzthiazolyl, isoxazolyl, pyrazolyl, triazolyl, tetrazolyl, indazolyl, 2,3-dihydrobenzofuranyl or 2,3-dihydrobenzothienyl;

n is independently at each occurrence 0, 1 or 2; and

m is independently at each occurrence 0-6;

with the provisos that:

(1) when R^4 is C_1-C_4 alkyl and Y is N, then Z is N;

(2) when R^3 is phenyl, Y is N, and Z is CH, at least one R^8 is other than dimethylamino or -$NCH_3C(O)CH_3$;

(3) when Z and K are CH, R^5 is -OR^7, and R^7 is CH_2R^{11}, then R^{11} is not CO_2R9; and

(4) when Y and Z are both N, K is CH, and R^3 is phenyl, then R1 is not chloro or fluoro.

[3] In a more preferred embodiment, the present invention provides a novel compound of formula I, wherein:

K is CR^5;

Y is N;

Z is CH or N;

R^1 is methyl;

R^3 is an phenyl moiety substituted with 1-3 substituents independently selected from the group consisting of: halo, methoxy, nitro, trifluoromethyl, methyl, amino, methylamino, dimethylamino, cyano, 4-tetrazolyl, carboxy, methylthio, methylsulfonyl, dichloro;

R^4 is ethyl;

R^5 is selected from the group consisting of C_{1-4} alkyl, C_{1-4} alkoxy, halo, acetyl, dimethylamino, cyano, methylthio, methylsulfonyl.

[4] In an even more preferred embodiment, the present invention provides a novel compound of formula I, wherein:

K is CR^5;

Y is CR^2;

Z is CH or N;

R^1 is methyl;

R^2 taken together with R^4 is -A=D-, where A and D are each CMe or N oriented in such a way as to form an imidazole or a triazole ring, or A is NR^9 and D is C=O oriented in such a way as to form an imidazolone;

R^3 is an phenyl moiety substituted with 1-3 substituents independently selected from the group consisting of trifluoromethyl, methyl, chloro; and

R^5 is selected from the group consisting of C_{1-4} alkyl, C_{1-4} alkoxy, halo, acetyl, dimethylamino, cyano, methylthio, methylsulfonyl.

[5] In another preferred embodiment, the present invention provides a novel compound of formula I, wherein the compound is selected from the group:

N-(2-Bromo-(1-methylethyl)phenyl)-N-ethyl-4-(2-chlorophenyl)-6-methyl-2-pyrimidineamine;

N-(2-Bromo-4,6-dimethoxyphenyl)-N-ethyl-4-(2-(trifluoromethy)phenyl)-6-methyl-2-pyrimidineamine;

N-(2-Bromo-4-(1-methylethyl)phenyl)-N-ethyl-4-(2-(trifluoromethyl)phenyl)-6-methyl-2-pyrimidineamine;

N-(2-Bromo-4-dimethylamino-6-methoxyphenyl)-N-ethyl-4-(2-(trifluoromethyl)phenyl)-6-methyl-2-pyrimidineamine;

N-(2-Bromo-4-(1-methylethyl))-N-ethyl-4-(3-(trifluoromethyl)phenyl)-6-methyl-2-pyrimidineamine;

N-(2-Bromo-4,6-dimethoxyphenyl)-N-ethyl-4-(2-chlorophenyl)-6-methyl-2-pyrimidineamine;

N-[2-Bromo-4-(1-methylethyl)phenyl]-N-ethyl-4-(2-nitrophenyl)-6-methyl-2-pyrimidineamine;

N-(2,4-Dibromophenyl)-N-ethyl-4-[2-(trifluoromethyl)phenyl]-6-methyl-2-pyrimidineamine;

N-(4-Acetyl-2-bromophenyl)-N-ethyl-4-[2-(trifluoromethyl)phenyl]-6-methyl-2-pyrimidineamine;

N-[2-Bromo-4-(1-methylethyl)phenyl]-N-ethyl-4-(2-cyanophenyl)-6-methyl-2-pyrimidineamine;

N-(2-Bromo-4-methylthiophenyl)-N-ethyl-4-[2-(trifluoromethyl)phenyl]-6-methyl-2-pyrimidineamine;

N-(2-Bromo-4-methylsulfonylphenyl)-N-ethyl-4-[2-(trifluoromethyl)phenyl]-6-methyl-2-pyrimidineamine;

N-[2-Bromo-4-(1-methylethyl)phenyl]-N-ethyl-4-(2,4,6-trimethylphenyl)-6-methyl-2-pyrimidineamine;

N-(2,4-Dibromophenyl)-N-ethyl-4-(2-methylthiophenyl)-6-methyl-2-pyrimidineamine;

N-(2-Bromo-4-(1-methylethyl)phenyl)-N-ethyl-4-(2-(trifluoromethyl)phenyl)-6-methyl-1,3,5-triazine-2-amine;

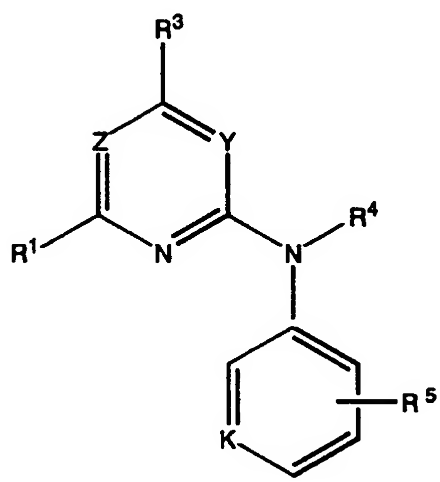
N-(4-dimethylamino-2-(trifluoromethyl)phenyl)-N-ethyl-4-(2-(trifluoromethyl)phenyl)-6-methyl-1,3,5-triazine-2-amine;

9-(2-Bromo-4,-isopropylphenyl)-2-methyl-6-(2-trifluoromethyl)phenyl)-8-azapurine and

N-(2-Bromo-4-(1-methylethyl)phenyl)-N-ethyl-4-(2-methylphenyl)-6-methyl-2-pyrimidineamine; and

N-(2-Bromo-4-)-(1-methylethyl)phenyl)-N-ethyl-4-(2,6-dichlorophenyl)-6-methyl-2-pyrimidineamine.

[6] In a third embodiment, the present invention provides a novel pharmaceutical composition, comprising: a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of formula (I):



(I)

or a stereoisomer or pharmaceutically acceptable salt form thereof, wherein:

Y is CR^2 or N;

Z is CH or N;

K is CR^5 or N;

R^1 is C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, chloro, fluoro, cyano, or trifluoromethyl;

R^2 taken together with R^4 is -E-F-, where E and F are independently CR^9 and CR^{9a}; or R^2 taken together with R^4 is -A=D-, where A and D are each independently CH, CR^{10} or N; provided that -A=D- may not be -CH=N- or CR^{10}=N- oriented in such a way as to form a pyrazole ring, but may be -CH=N- or CR^{10}=N- oriented in such a way as to form an imidazole ring; or R^2 taken together with R^4 is -A-D- where A is NR^9 and D is C=O oriented in such a way as to form an imidazolone.

R^3 is phenyl substituted on 1-4 ring carbons with R^8, napthyl substituted on 1-4 ring carbons with R^8, pyridinyl substituted on 1-4 ring carbons with R^8, or pyrimidinyl substituted on 1-3 ring carbons with R^8;

R^4 is C_1-C_4 alkyl, allyl, or propargyl, where C_1-C_4 alkyl is optionally substituted with C_3-C_6 cycloalkyl, OH, $-OR^9$, $-S(O)_nR^9$ or $-CO_2R^9$;

R^5 represents 1-4 substituents on ring carbons each of which may be independently C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_6 cycloalkyl, C_4-C_{10} cycloalkylalkyl, halo,

nitro,cyano, $-NR^6R^7$, $-OR^7$, $-COR^7$, $-C(O)NR^6R^7$, $-C(NOR^9)R^7$, or $-S(O)_nR^7$, where C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_6 cycloalkyl and C_4-C_{10} cycloalkylalkyl are optionally substituted with 1 to 3 substituents independently selected from halo, nitro, cyano, $-NR^6R^7$, $-OR^7$, $-COR^7$, $-C(O)NR^6R^7$, $-S(O)_nR^7$, and $-C(NOR^9)R^7$ and two R^5 moieties taken together may comprise $CR^9R^{9a}CR^9R^{9a}O$, $CR^9R^{9a}CR^9R^{9a}CR^9R^{9a}$, or $CR^9{=}CR^{9a}O$;

R^6 and R7 are independently at each occurrence H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, $-(CH_2)_m$-phenyl, or $-(CH_2)_m$-heteroaryl; all optionally substituted with 1-3 R^{11}'s.

R^8 is independently at each occurrence C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_4-C_{10} cycloalkylalkyl, phenyl, heteroaryl, halo, nitro,cyano, $-NR^6R^7$, $-OR^7$, $-COR^7$, $-CO_2R^7$, $-C(O)NR^6R^7$, $-OC(O)NR^6R^7$, $-NR^9C(O)NR^6R^7$, $-NR^6C(O)R^7$, $-C(NOR^9)R^7$, $-S(O)_nR^7$, $-NR^9SO_2R^7$, $-SO_2NR^6R^7$, and where C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_4-C_{10} cycloalkylalkyl, and phenyl are optionally substituted with 1 to 3 substituents independently selected from halo, nitro, cyano, $-NR^6R^7$, $-OR^7$, $-COR^7$, $-C(O)NR^6R^7$, $-S(O)_nR^7$, $-C(NOR^9)R^7$, $-NR^9SO_2R^7$, and $-SO_2NR^6R^7$; provided that when R^3 is pyridinyl, at least one R^8 is other than methyl; further provided that when R^3 is phenyl, at least one R^8 is other than unsubstituted phenyl;

R^9 and R^{9a} is H or C_1-C_4 alkyl;

R^{10} is C_1-C_4 alkyl, halo, nitro, cyano, $-NR^9R^{9a}$, $-OR^{12}$, or $-S(O)_nR^{12}$;

R^{11} is independently at each occurrence C_1-C_3 alkyl, halo, nitro, cyano, $-NR^9R^{9a}$, $-OR^9$ $-S(O)_nR^{12}$, $-COR^9$, $-CO_2R^9$, $-C(O)NR^9R^{9a}$, $-NR^9C(O)R^{9a}$, or $-C(NOR^9)R^{9a}$.

R^{12} is C_1-C_4 alkyl;

heteroaryl is pyridyl, pyrimidinyl, triazinyl, furanyl, quinolinyl, isoquinolinyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrrolyl, oxazolyl, benzofuranyl, benzothienyl, benzthiazolyl, isoxazolyl, pyrazolyl, triazolyl, tetrazolyl, indazolyl, 2,3-dihydrobenzofuranyl or 2,3-dihydrobenzothienyl;

n is independently at each occurrence 0, 1 or 2; and

m is independently at each occurrence 0-6.

Many compounds of this invention have one or more asymmetric centers or planes. Unless otherwise indicated, all chiral (enantiomeric and diastereomeric) and racemic forms are included in the present invention. Many geometric isomers of olefins, C=N double bonds, and the like can also be present in the compounds, and all such stable isomers are contemplated in the present invention. The compounds may be isolated in optically active or racemic forms. It is well known in the art how to prepare optically active forms, such as by resolution of racemic forms or by synthesis from optically active starting materials. All chiral, (enantiomeric and diastereomeric) and racemic forms and all geometric isomeric forms of a structure are intended, unless the specific stereochemistry or isomer form is specifically indicated.

The term "alkyl" includes both branched and straight-chain alkyl having the specified number of carbon atoms. "Alkenyl" includes hydrocarbon chains of either a straight or branched configuration and one or more unsaturated carbon-carbon bonds which may occur in any stable point along the chain, such as ethenyl, propenyl, and the like. "Alkynyl" includes hydrocarbon chains of either a straight or branched configuration and one or more triple carbon-carbon bonds which may occur in any stable point along the chain, such as ethynyl, propynyl and the like. "Haloalkyl" is intended to include both branched and straight-chain alkyl having the specified number of carbon atoms, substituted with 1 or more halogen; "alkoxy" represents an alkyl group of indicated number of carbon atoms attached through an oxygen bridge; "cycloalkyl" is intended to include saturated ring groups, including mono-,bi- or poly-cyclic ring systems, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and so forth. "Halo" or "halogen" includes fluoro, chloro, bromo, and iodo.

The term "substituted", as used herein, means that one or more hydrogen on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency is not exceeded, and that the substitution results in a stable compound. When a substitent is keto (i.e., =O), then 2 hydrogens on the atom are replaced.

Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. By "stable compound" or "stable structure" is meant a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

The term "appropriate amino acid protecting group" means any group known in the art of organic

synthesis for the protection of amine or carboxylic acid groups. Such amine protecting groups include those listed in Greene and Wuts, "Protective Groups in Organic Synthesis" John Wiley & Sons, New York (1991) and "The Peptides: Analysis, Synthesis, Biology, Vol. 3, Academic Press, New York (1981), the disclosure of which is hereby incorporated by reference. Any amine protecting group known in the art can be used. Examples of amine protecting groups include, but are not limited to, the following: 1) acyl types such as formyl, trifluoroacetyl, phthalyl, and p-toluenesulfonyl; 2) aromatic carbamate types such as benzyloxycarbonyl (Cbz) and substituted benzyloxycarbonyls, 1-(p-biphenyl)-1-methylethoxycarbonyl, and 9-fluorenylmethyloxycarbonyl (Fmoc); 3) aliphatic carbamate types such as tert-butyloxycarbonyl (Boc), ethoxycarbonyl, diisopropylmethoxycarbonyl, and allyloxycarbonyl; 4) cyclic alkyl carbamate types such as cyclopentyloxycarbonyl and adamantyloxycarbonyl; 5) alkyl types such as triphenylmethyl and benzyl; 6) trialkylsilane such as trimethylsilane; and 7) thiol containing types such as phenylthiocarbonyl and dithiasuccinoyl.

The term "amino acid" as used herein means an organic compound containing both a basic amino group and an acidic carboxyl group. Included within this term are natural amino acids, modified and unusual amino acids, as well as amino acids which are known to occur biologically in free or combined form but usually do not occur in proteins. Included within this term are modified and unusual amino acids, such as those disclosed in, for example, Roberts and Vellaccio (1983) <u>The Peptides</u>, 5: 342-429, the teaching of which is hereby incorporated by reference. Modified or unusual amino acids which can be used to practice the invention include, but are not limited

to, D-amino acids, hydroxylysine, 4-hydroxyproline, an N-Cbz-protected amino acid, ornithine, 2,4-diaminobutyric acid, homoarginine, norleucine, N-methylaminobutyric acid, naphthylalanine, phenylglycine, ß-phenylproline, tert-leucine, 4-aminocyclohexylalanine, N-methyl-norleucine, 3,4-dehydroproline, N,N-dimethylaminoglycine, N-methylaminoglycine, 4-aminopiperidine-4-carboxylic acid, 6-aminocaproic acid, trans-4-(aminomethyl)-cyclohexanecarboxylic acid, 2-, 3-, and 4-(aminomethyl)-benzoic acid, 1-aminocyclopentanecarboxylic acid, 1-aminocyclopropanecarboxylic acid, and 2-benzyl-5-aminopentanoic acid.

The term "amino acid residue" as used herein means that portion of an amino acid (as defined herein) that is present in a peptide.

The term "peptide" as used herein means a compound that consists of two or more amino acids (as defined herein) that are linked by means of a peptide bond. The term "peptide" also includes compounds containing both peptide and non-peptide components, such as pseudopeptide or peptide mimetic residues or other non-amino acid components. Such a compound containing both peptide and non-peptide components may also be referred to as a "peptide analog".

The term "peptide bond" means a covalent amide linkage formed by loss of a molecule of water between the carboxyl group of one amino acid and the amino group of a second amino acid.

The term "pharmaceutically acceptable salts" includes acid or base salts of the compounds of formulas (I) and (II). Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like.

Pharmaceutically acceptable salts of the compounds of the invention can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, PA, 1985, p. 1418, the disclosure of which is hereby incorporated by reference.

"Prodrugs" are considered to be any covalently bonded carriers which release the active parent drug of formula (I) or (II) *in vivo* when such prodrug is administered to a mammalian subject. Prodrugs of the compounds of formula (I) and (II) are prepared by modifying functional groups present in the compounds in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent compounds. Prodrugs include compounds wherein hydroxy, amine, or sulfhydryl groups are bonded to any group that, when administered to a mammalian subject, cleaves to form a free hydroxyl, amino, or sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of alcohol and amine functional groups in the compounds of formulas (I) and (II); and the like.

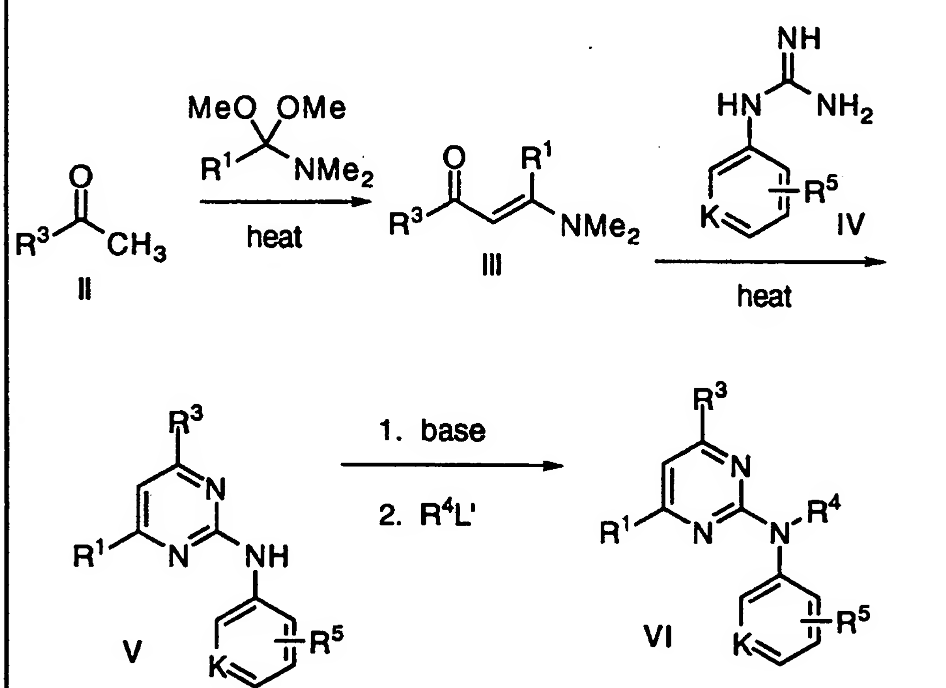
The term "therapeutically effective amount" of a compound of this invention means an amount effective to antagonize abnormal levels of CRF or treat the symptoms of affective disorder, anxiety, depression, immunological, cardiovascular or heart-related diseases and colonic hypersensitivity associated with psychopathological disturbance and stress in a host. in a host.

Synthesis

The compounds of the present invention can be prepared by one of the general schemes outlined below.

Compounds of the Formula (I), wherein Z is CH, and Y is N, and R^1 is C_1-C_4 alkyl can be prepared as shown in Scheme 1.

Scheme 1

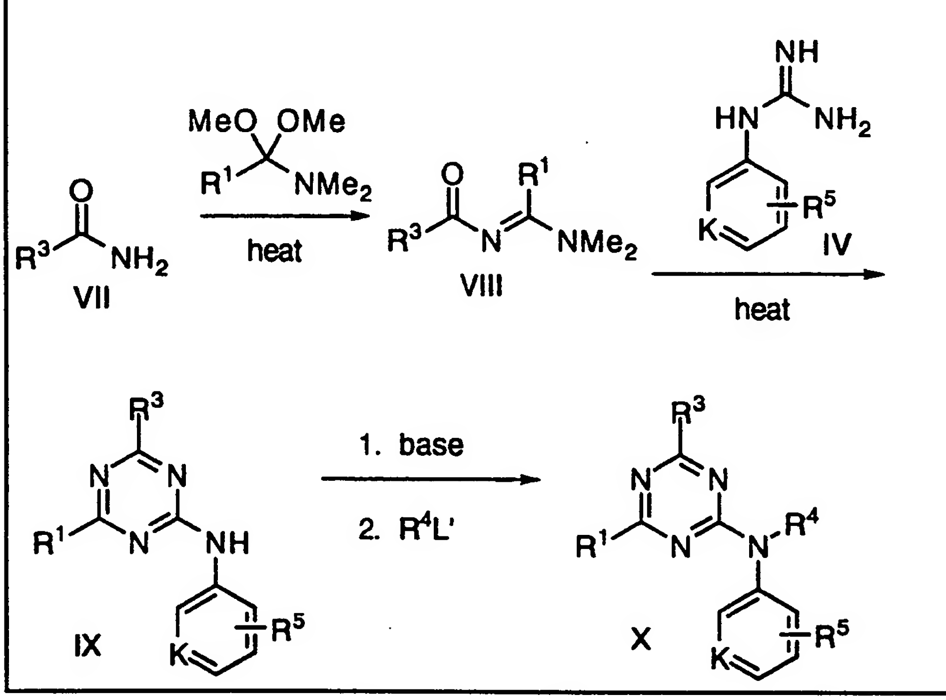


A methyl ketone (II) was converted to the enaminoketone (III) by treatment with a dimethylamide dimethyl acetal as described in U. S. Patent 4,788,195 (Torley et al). Most preferably, (II) was treated with dimethylamide dimethyl acetal in the absence of solvent at temperatures from 80° to reflux. The enaminoketone (III) was reacted with an aryl or heteroaryl guanidine (IV), (in the presence of a base such as potassium carbonate if the guanidine is used as a salt) in N,N-dimethylformamide (DMF) or an alcoholic solvent to afford the corresponding

pyrimidine (V). This was treated with a base such as sodium hydride (NaH) or lithium diisopropylamide (LDA) in an aprotic solvent such as tetrahydrofuran (THF), dimethylformamide (DMF), or dimethyl sulfoxide (DMSO) followed by an alkylating agent R^4L', such as an alkyl iodide, mesylate or tosylate to afford (VI) the corresponding alkylated product of Formula (I).

Compounds of Formula (I), wherein Y and Z are both N and R^1 is C_1-C_4 alkyl can be prepared as shown in Scheme 2.

Scheme 2

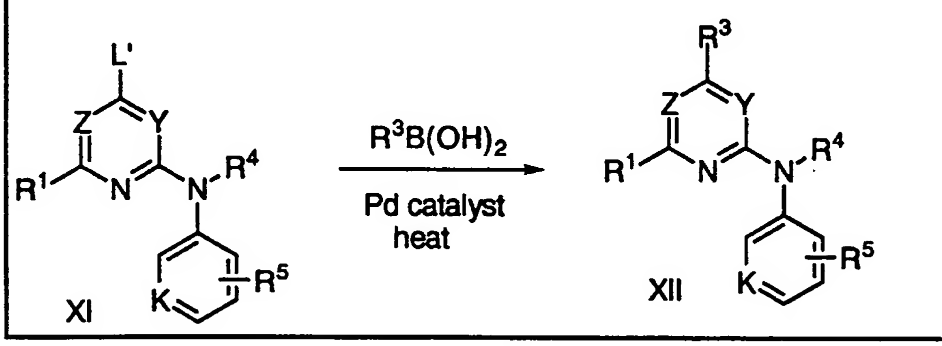


A primary amide (VII) can be converted to an acylamidine (VIII) by treatment with dimethylamide dimethyl acetal . Most preferably, (VII) is treated with dimethylamide dimethyl acetal in the absence of solvent at temperatures from 50° to reflux. The acylamidine (VIII) is reacted with an aryl or heteroaryl guanidine in N,N-dimethylformamide (DMF) or an alcoholic solvent to afford the corresponding

triazine (IX). This is subsequently alkylated to afford (X), a compound of Formula (1).

The compounds of Formula (1) where R^3 is aryl or heteroaryl, and where Z and Y are each independently CH, CR^2, or N; and R^2 is C1 to C_4 alkyl, chloro, or cyano; or R^2 at the Y position taken together with R^4 is -A=D-, where A and D are each independently CH, CR^1, or N, where R^1 is not halo, can be prepared as shown in Scheme 3.

Scheme 3

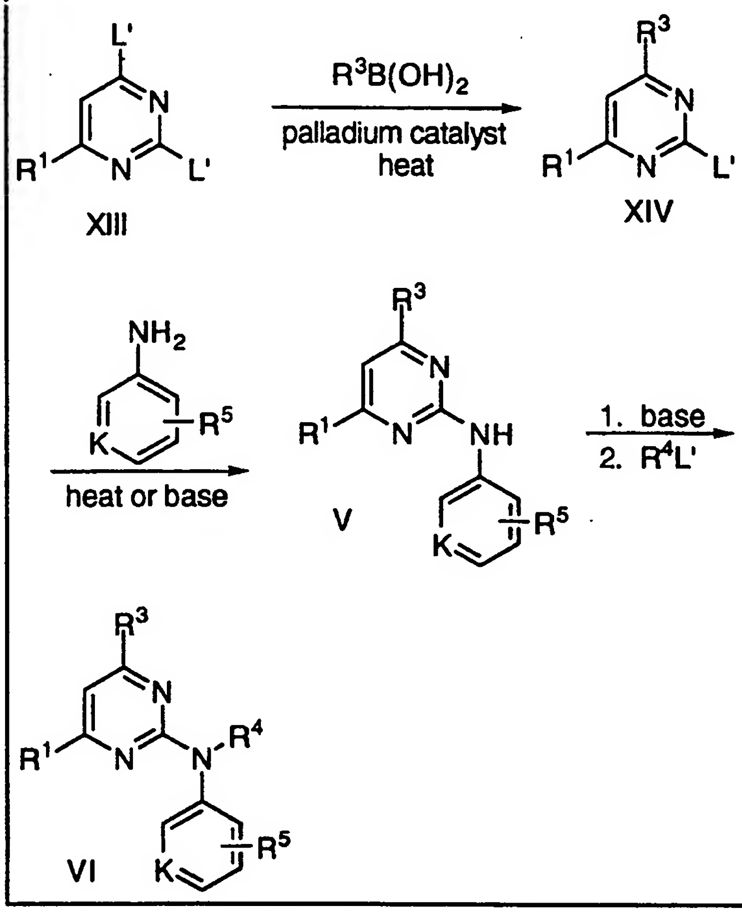


The compound (XI), in which L' is a leaving group such as chloro, bromo, tosyl, mesyl, or triflyl, was treated in an organic solvent such as benzene, toluene, xylene, or dimethoxyethane with an aryl or heteroaryl boronic acid in the presence of a palladium catalyst such as but not limited to tetrakis(triphenylphosphine)palladium , bis(triphenylphosphine)palladium dichloride, or palladium acetate and a base such as aqueous sodium bicarbonate, sodium carbonate, sodium hydroxide, barium hydroxide, or cesium fluoride to afford the arylated or heteroarylated product (XII), a compound of Formula (1). Most preferably, (XI) is treated with boronic acid in refluxing mixture of benzene and ethanol, an aqueous base such as sodium carbonate, and tetrakis(triphenylphosphine)palladium (0).

The heterocyclic chlorides (XI) required for this procedure are described in the patent literature. The preparation of the pyrimidine, 1,3,5-triazine, 8-azapurine, purine, and azaindole chlorides are described in Patent Application WO 95/10506 (Aldrich *et al*), while the synthesis of pyrrolo[2,3-d]pyrimidine chlorides are described in patent application WO 94/13676 (Y. L. Chen) and pyrazolo[3,4-d]pyrimidine chlorides are described in patent application WO 94/13677 (Y. L. Chen). Aryl boronic acids are available commercially or may be synthesized by a variety of methods which have been reviewed by N. Miyaura and A. Suzuki, Chemistry Reviews, **95**, 2457 (1995).

Pyrimidine compounds of Formula (1) may also be prepared as shown in Scheme 4.

Scheme 4

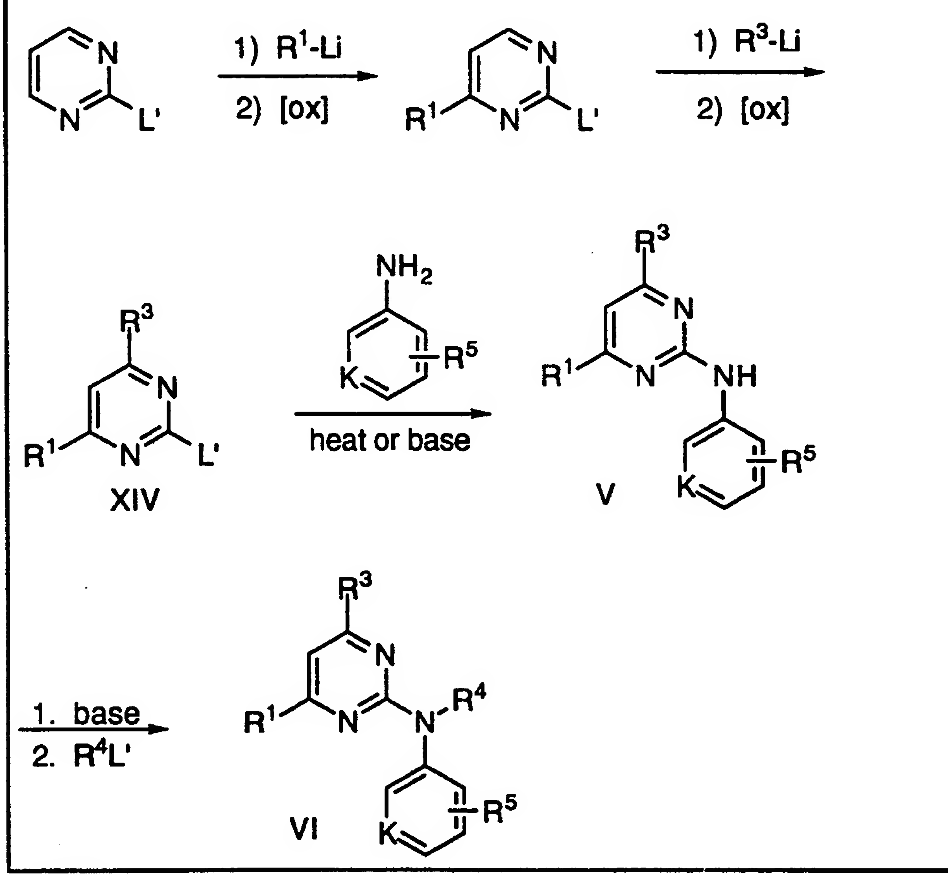


A pyrimidine (XIII) with two leaving groups such as 2,4-dichloro-6-methylpyrimidine was treated with an aryl or heteroaryl boronic acid in the presence of a palladium catalyst to afford the arylated or heteroarylated pyrimidine (XIV). This was reacted with the appropriate aniline or heteroaryl amine in a high-boiling solvent, such as, but not limited to, ethylene glycol, methoxyethoxyethanol etc., or in an aprotic solvent such as THF, dioxane, toluene, xylene, or DMF facilitated by the optional use of a base such as sodium hydride or LDA, which are preferred. The coupled product (V) was subsequently alkylated as described above to afford (VI), a compound of Formula (1). The anilines required for this procedure are

either commercially available, or may be synthesized by methods described in Patent Application WO 95/10506 (Aldrich *et al*).

Compounds of Formula (1) which are pyrimidines may also be prepared as shown in Scheme 4a.

Scheme 4a

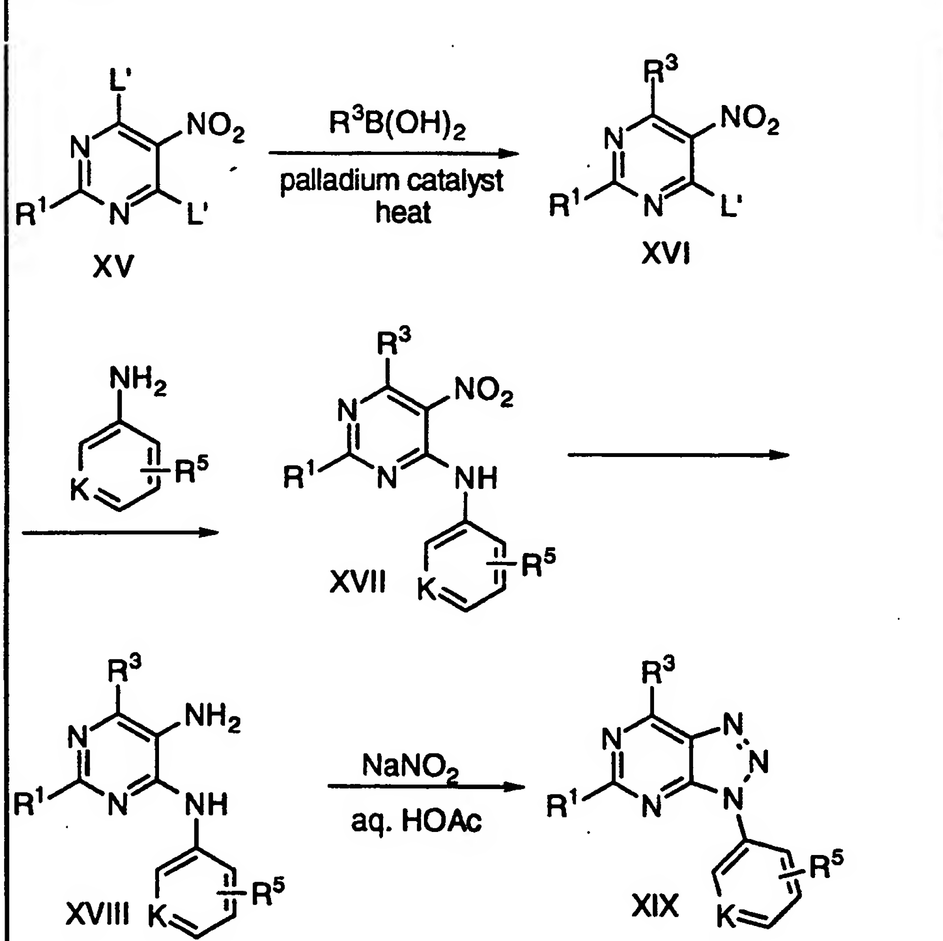


R^1 and/or R^3 can be attached in either order to the 4- and/or 6-positions by adding an aryl- or alkyllithium reagent and the oxidizing the intermediate dihydropyrimidine. When not commercially available, the required aryl- and alkyllithium reagents can be prepared by conventional methods such as deprotonation, halogen-metal exchange, transmetallation, or by treating a halide with lithium metal. As described by Strekowski et al (J.

Heterocylic Chem. 27, 1393 (1990), despite the presence of a leaving group in the 2-position, attack occurs at an unsubstituted 4- or 6-position in preference to the 2-position. As described above, the resulting pyrimidines (XIV) can be coupled with an aniline or heterocyclic amine and N-alkylated to produce compounds (VI) of Formula (1).

Compounds of Formula (1) which are 8-azapurines may be prepared as shown in Scheme 5.

Scheme 5

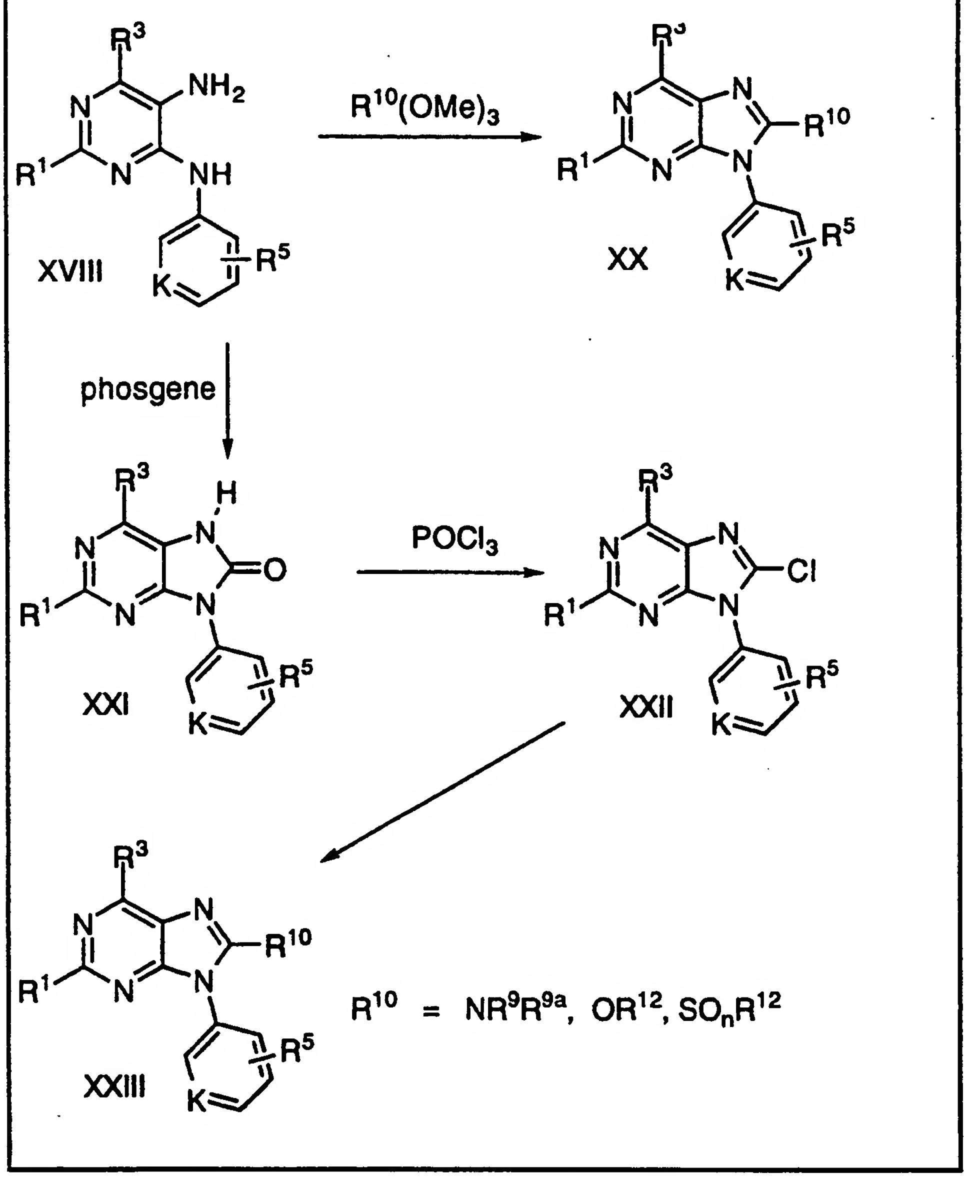


A 5-nitropyrimidine (XV) with two leaving groups such as a 4,6-dichloro-5-nitropyrimidine [J. Chem. Soc. 3832 (1954); ibid. 677 (1944)] was treated with an

aryl or heteroaryl boronic acid in the presence of a palladium catalyst to afford the arylated or heteroarylated pyrimidine (XVI). This was reacted with the appropriate aniline or heteroaryl amine in an appropriate solvent, such as, but not limited to, THF, dioxane, toluene, xylene, or DMF facilitated by the optional use of a base such as triethylamine, diisopropylethylamine, sodium hydride or LDA. The nitro group of the coupled product (XVII) can be reduced by catalytic hydrogenation or with a variety of reducing agents such as stannous chloride, sodium dithionite, or iron in acetic acid, to afford a 5-aminopyrimidine (XVIII). This can be converted with sodium nitrite in aqueous acetic acid to the 8-azapurine (XIX), a compound of Formula (1).

Purines may be prepared as shown in Scheme 6.

Scheme 6



The 5-aminopyrimidine (XIII) can be converted into Purine (XX) where R^{10} is H or alkyl by treatment with an orthoester. Reaction of (XVIII) with a reagent such as phosgene, carbonyldiimidazole, or diethylcarbonate affords a purinone (XXI). Treatment of the purinone with phosphorous oxychloride can give the 8-chloropurine (XXII), a compound of Formula (1) which can in turn be converted by methods well known

in the art into a 8-dialkylaminopurine , an 8-alkoxypurine , and an 8-alkylthiopurine (XXIII), by treatment with a dialkylamine, a metal alkoxide such as a sodium alkoxide, or a metal thioalkoxide, respectively. The 8-alkylthiopurines can in turn be converted into the corresponding sulfoxide and sulfone by oxidation methods well known in the art.

The following examples are provided to describe the invention in further detail. These examples, which set forth the best mode presently contemplated for carrying out the invention, are intended to illustrate and not to limit the invention.

Example 1

Preparation of N-(2-Bromo-4-(1-methylethyl)phenyl)-N-ethyl-4-(2-bromophenyl)-6-methyl-2-pyrimidineamine

Part A: A mixture of 2-bromoacetophenone (7 g) and dimethylacetamide dimethyl acetal (14 mL) was refluxed for 5 hrs, and the cooled reaction mixture was concentrated *in vacuo*. The crude reaction product was purified by evaporative distillation (0.1 mm / 150°) to afford a dark orange liquid (10.2 g) of sufficient purity for further reaction. A portion of this material was purified further by chromatography on silica gel using from 20% ethyl acetate in hexanes to 100% ethyl acetate as eluent to afford the intermediate enaminoketone (2 g) as an amorphous yellow solid. ^{1}HNMR ($CDCl_3$), 300 MHz) δ 7.54 (dd, 1H, J = 7.7, 1.1 Hz), 7.38 (dd, 1H, J = 7.7, 1.1 Hz), 7.29 (dt, 1H, J = 7.3, 1.1 Hz), 7.16 (dt, 1H, J = 7.4, 1.1 Hz), 5.22 (s, 1H), 3.04 (bs, 6H), 2.67 (s, 3H).

Part B: A mixture of the product from part A (1.09 g), 2-bromo-4-isopropylphenylguanidine hydrochloride (1.17 g), and sodium carbonate (424 mg) in 2-methoxyethanol (30 mL) was refluxed for 19 hr. The cooled reaction mixture was diluted with ethyl acetate and washed with water (2X) and brine, dried and evaporated. The crude reaction product was chromatographed on silica gel using 50% petroleum ether in methylene chloride as eluent. The intermediate anilinopyrimidine was obtained as an oil (337 mg). CI Mass Spec. $(M+H)^+ = 462$.

Part C: To a solution of the product from part B (320 mg) in dry dimethylsulfoxide (9 mL) was added 100% sodium hydride (40 mg) and iodoethane (0.300 mL). The reaction mixture was stirred for 1.5 hr, and then poured onto brine. This mixture was extracted twice with ethyl acetate, and concentrated *in vacuo* to 320 mg of a dark oil. The crude product was purified by preparative thin layer chromatography on 4 2mm thick silica gel plates eluted with 50% petroleum ether in methylene chloride. The title compound was obtained as a pale yellow oil (260 mg). CI-HRMS calcd. for $C_{22}H_{24}N_3Br_2$ (M+H): 488.033695. Found: 488.032196.

Example 2

Preparation of N-(2-Bromo-(1-methylethyl)phenyl)-N-ethyl-4-(2-chlorophenyl)-6-methyl-2-pyrimidineamine

The title compound was prepared in a manner similar to the product of Example 1. Elemental Analysis: Calcd. for $C_{22}H_{23}N_3ClBr$: C, 59.41: H, 5.21; N, 9.456. Found: C, 59.51; H, 5.21; N, 8.97.

Example 3

Preparation of N-(2-Bromo-4-dimethylamino-6-methoxyphenyl)-N-ethyl-4-(2-chlorophenyl)-6-methyl-2-pyrimidineamine

The title compound was prepared in a manner similar to the product of Example 1, mp 131-132° Elemental Analysis: Calcd. for $C_{22}H_{24}N_4OClBr$: C, 55.53: H, 5.08; N, 11.77. Found: C, 55.40; H, 5.17; N, 11.60.

Example 4

N-(2-Bromo-4,6-dimethoxyphenyl)-N-ethyl-4-(2-(trifluoromethyl)phenyl)-6-methyl-2-pyrimidineamine

Part A: A mixture of 2,4-dichloro-6-methylpyrimidine (3.26 g, Aldrich), 2-(trifluoromethyl)phenylboronic acid (4.00 g), tetrakis(triphenylphosphine)palladium(0) (500 mg), 1M aqueous sodium carbonate (22 mL), and benzene (60 mL) was refluxed for 7 hr. The cooled mixture was diluted with ethyl acetate and the aqueous layer was removed. The organic layer was washed with water (2X) and brine, dried and concentrated *in vacuo*. The crude reaction product was chromatographed on silica gel using ethyl acetate / hexanes (1:5) as eluent. The intermediate arylpyrimidine was obtained as a white solid (3.35 g). ^{1}HNMR ($CDCl_3$), 300 MHz) δ 7.80 (d, 1H, J = 7.0 Hz), 7.64 (m, 2H), 7.51 (d, 1H, J = 7.3 Hz), 7.27 (s, 1H), 2.61 (s, 3H).

Part B: A mixture of the product from Part A (300 mg), 2-bromo-4,6-dimethoxyaniline (275 mg) and 100% sodium hydride (75 mg) in dry toluene (8 mL). was refluxed for 5 hr. The excess sodium hydride in the cooled reaction mixture was quenched with a small amount

of sodium hydride, and the mixture was partitioned between water and ethyl acetate. The organic layer was washed with brine, dried and evaporated *in vacuo*, and the crude reaction product was chromatographed on silica gel using ethyl acetate / hexanes (1:4) as eluent. The intermediate anilinopyrimidine was obtained as a pale yellow oil (255 mg). CI Mass Spec. $(M+H)^+$ = 468, 470.

Part C: To a solution of the product from Part B (250 mg) in dry dimethylsulfoxide (6 mL) was added 100% sodium hydride (40 mg) and iodoethane (0.250 mL). The reaction mixture was stirred for 30 min, quenched with a small amount of methanol, and then poured onto water. This mixture was extracted twice with ethyl acetate, and the combined extracts were washed with brine, dried, and concentrated *in vacuo* to 210 mg of a dark oil. The crude product was purified by preparative thin layer chromatography on 4 2mm thick silica gel plates eluted with 25% ethyl acetate in hexanes. The title compound was obtained as an oil (150 mg) which crystallized from ether - petroleum ether to afford colorless crystals (110 mg). mp 137-138°. CI-HRMS calcd. for $C_{22}H_{22}N_3O_2F_3Br$ (M+H): 496.08748. Found: 496.083703.

Example 5

Preparation of N-(2-Bromo-4-(1-methylethyl)phenyl)-N-ethyl-4-(2-(trifluoromethyl)phenyl)-6-methyl-2-pyrimidineamine

The title compound was prepared in a manner similar to the product of Example 4, mp 101.2-102.5°. Elemental Analysis: Calcd. for $C_{23}H_{23}N_3F_3Br$: C, 57.75: H, 4.856; N, 8.78. Found: C, 58.03; H, 4.90; N, 8.73.

Example 6

Preparation of N-(2-Bromo-4-dimethylamino-6-methoxyphenyl)-N-ethyl-4-(2-(trifluoromethyl)phenyl)-6-methyl-2-pyrimidineamine

The title compound was prepared in a manner similar to the product of Example 4, mp 157-158.5°. Elemental Analysis: Calcd. for $C_{23}H_{24}OF_3Br$: C, 54.23: H, 4.759; N, 11.00. Found: C, 53.78; H, 4.74; N, 10.75.

Example 7

Preparation of N-(2-Bromo-4-(1-methylethyl))-N-ethyl-4-(3-(trifluoromethyl)phenyl)-6-methyl-2-pyrimidineamine

The title compound was prepared in a manner similar to the product of Example 4. Elemental Analysis: Calcd. for $C_{23}H_{23}N_3F_3Br$: C, 57.75: H, 4.856; N, 8.78. Found: C, 58.01; H, 4.71; N, 8.76.

Example 8

Preparation of N-(2-Bromo-4-(1-methylethyl)phenyl)-N-ethyl-4-(4-(trifluoromethyl)phenyl)-6-methyl-2-pyrimidineamine

The title compound was prepared in a manner similar to the product of Example 4. Elemental Analysis: Calcd. for $C_{23}H_{23}N_3F_3Br$: C, 57.75: H, 4.856; N, 8.78. Found: C, 57.66; H, 4.78; N, 8.68.

Example 9

Preparation of N-(2-Bromo-4-(1-methylethyl)phenyl)-N-ethyl-4-(2-fluorophenyl)-6-methyl-2-pyrimidineamine

The title compound was prepared in a manner similar to the product of Example 4. Elemental Analysis: Calcd. for $C_{22}H_{23}N_3FBr$: C, 61.69: H, 5.41; N, 9.819. Found: C, 61.56; H, 5.12; N, 9.73.

Example 10

Preparation of N-(2-Bromo-4,6-dimethoxyphenyl)-N-ethyl-4-(2-chlorophenyl)-6-methyl-2-pyrimidineamine

Part A: To a solution of 2-bromo-4,6-dimethoxyaniline (1.16 g) in 10 mL ether was added 6 mL 1N HCl/ether. A precipitate formed and the mixture was concentrated to dryness. To the solid was added ethanol (20 mL), water (20 mL), and cyanamide (673 mg) and the reaction was heated at reflux for 90 minutes. Added 4M HCl/dioxane (2 mL) and cyanamide (673 mg) and heated at reflux for 2 h. Solvent was removed *in vacuo* and the residue was taken up in 1M pH7 buffer (100mL) and ether (100mL). The layers were separated and the aqueous layer was washed further with 2 portions (100mL each) of ether. The pH of the aqueous layer was adjusted to 13 with solid sodium hydroxide and extracted with 3 portions (100 mL each) of methylene chloride which were combined and concentrated to dryness to afford (2-bromo-4,6-dimethoxyphenyl)guanidine (1.33 g). ^1H-NMR ($CDCl_3$, 300 MHz), δ 6.80 (d, 1H, J = 2.9 Hz), 6.53 (d, 1H, J = 2.6 Hz), 4.62 (broad s, 4H), 3.85 (s, 6H).

Part B: The title compound was prepared using the product of part A in a manner similar to the product of Example 1. Elemental analysis: Calcd. for $C_{21}H_{21}N_3O_2ClBr$: C, 54.50; H, 4.57; N, 9.08; Cl, 7.66. Found: C, 54.21; H, 4.65; N, 8.82; Cl, 7.95.

Example 11

Preparation of N-[2-Bromo-4-(1-methylethyl)phenyl]-N-ethyl-4-(2-nitrophenyl)-6-methyl-2-pyrimidineamine

The title compound was prepared in a manner similar to the product of Example 1. Elemental analysis: Calcd. for $C_{22}H_{23}N_4O_2Br$: C, 58.03; H, 5.09; N, 12.30; Br, 17.55. Found: C, 57.99; H, 5.06; N, 12.17; Br, 17.45.

Example 12

N-[2-Bromo-4-(1-methylethyl)phenyl]-N-ethyl-4-(2-aminophenyl)-6-methyl-2-pyrimidineamine

The product of Example 11 (778 mg), methanol (40.5 mL), acetic acid (13.5 mL) and iron powder (382 mg) were heated at reflux and stirred mechanically for 6 h. More iron powder (1.15 g)was added and the reaction was heated at reflux 2 more hours, after which it was cooled, filtered through celite, and concentrated to a thick black oil. Added ethyl acetate (200 mL) and water (100 mL), stirred, and filtered through celite. The layers were separated and the ethyl acetate dried over $MgSO_4$ and concentrated to a thick yellow oil (754 mg). The oil was chromatographed on silica gel using ethyl acetate/hexane (1:9) as eluent. The title compound was obtained as an off-white solid (526 mg). CI-HRMS calc'd. for $C_{22}H_{26}N_4Br$ $(M+H)^+$: 425.134083. Found: 425.131850.

Example 13

Preparation of N-[2-Bromo-4-(1-methylethyl)phenyl]-N-ethyl-4-(2-methylaminophenyl)-6-methyl-2-pyrimidineamine

and

Preparation of N-[2-Bromo-4-(1-methylethyl)phenyl]-N-ethyl-4-(2-dimethylaminophenyl)-6-methyl-2-pyrimidineamine

The product from Example 12 (288 mg), acetonitrile (20 mL), dimethyl sulfate (128 mg), and sodium bicarbonate (114 mg) were heated at reflux 4 hours. The reaction was concentrated and dissolved in methylene chloride (20 mL) and water (20 mL). The layers were separated and the aqueous layer was again extracted with methylene chloride (20 mL). The combined organic layers were dried and concentrated to a yellow foam (297 mg) which was chromatographed on silica gel using ethyl acetate/hexane (1:9) to afford *N*-[2-Bromo-4-(1-methylethyl)phenyl]-*N*-ethyl-4-(2-methylaminophenyl)-6-methyl-2-pyrimidineamine (61 mg) and *N*-[2-Bromo-4-(1-methylethyl)phenyl]-*N*-ethyl-4-(2-dimethylaminophenyl)-6-methyl-2-pyrimidineamine (55 mg). CI-HRMS calcd. for $C_{23}H_{28}N_4Br$ $(M+H)^+$: 439.149733. Found: 439.148138 (*N*-[2-Bromo-4-(1-methylethyl)phenyl]-*N*-ethyl-4-(2-methylaminophenyl)-6-methyl-2-pyrimidineamine). CI-HRMS calcd. for $C_{24}H_{30}N_4Br$ $(M+H)^+$: 453.165383. Found: 453.163184 (*N*-[2-Bromo-4-(1-methylethyl)phenyl]-*N*-ethyl-4-(2-dimethylaminophenyl)-6-methyl-2-pyrimidineamine).

Example 15

Preparation of N-(2,4-Dibromophenyl)-N-ethyl-4-[2-(trifluoromethyl)phenyl]-6-methyl-2-pyrimidineamine

The title compound was prepared in a manner similar to the product of Example 1. CI-HRMS calc'd for $C_{20}H_{17}N_3F_3Br_2$ $(M+H)^+$: 513.974130. Found: 513.972790.

Example 16

Preparation of N-(4-Acetyl-2-bromophenyl)-N-ethyl-4-[2-(trifluoromethyl)phenyl]-6-methyl-2-pyrimidineamine

The product of Example 15 (515 mg), bis(triphenylphosphine)Pd(II)dichloride (19 mg), and tetrakis(triphenylphosphine)Pd(0) (27 mg) were combined

in a round bottom flask and pumped and purged with nitrogen (3X). Added distilled toluene (2.5 mL), and pumped and purged with nitrogen (2X). Added 1-ethoxyvinyltri-*n*-butyl tin (0.41 mL), pumped and purged with nitrogen (1X), and heated at reflux 18 hours. Removed solvent *in vacuo*. Ether (15 mL) and 10% potassium fluoride (aq.) were added and stirred 15 minutes, filtered and the layers separated. The ether layer was dried over $MgSO_4$ and concentrated to dryness, giving the title compound (257 mg). CI-HRMS calcd. for $C_{22}H_{20}N_3OF_3Br$ $(M+H)^+$: 478.074183. Found: 478.072218.

Example 17

Preparation of N-[2-Bromo-4-(1-methylethyl)phenyl]-N-ethyl-4-(3-collidyl)-6-methyl-2-pyrimidineamine

The title compound was prepared in a manner similar to the product of Example 1. CI-HRMS calcd. for $C_{24}H_{30}N_4Br$ $(M+H)^+$: 453.165383. Found: 453.164255.

Example 18

Preparation of N-[2-Bromo-4-(1-methylethyl)phenyl]-N-ethyl-4-(2-cyanophenyl)-6-methyl-2-pyrimidineamine

The title compound was prepared in a manner similar to the product of Example 1. CI-HRMS calcd. for $C_{23}H_{24}N_4Br$ $(M+H)^+$: 435.118433. Found: 435.119074.

Example 19

Preparation of N-[2-Bromo-4-(1-methylethyl)phenyl]-N-ethyl-4-(2-tetrazolophenyl)-6-methyl-2-pyrimidineamine

The product from Example 18 (131 mg), trimethyl tin chloride (150 mg), sodium azide (50 mg), and toluene (2 mL) were heated at reflux for 18 hours. The reaction was concentrated to dryness, taken up in methylene chloride (10 mL) and water (10 mL) and filtered. The

organic layer was concentrated to dryness. The crude reaction product was chromatographed on silica gel using ethyl acetate/hexane (2:5) to ethyl acetate to methanol/methylene chloride (1:19), which afforded the title compound (50 mg). CI-HRMS calcd. for $C_{23}H_{25}N_7{}^{81}Br$ $(M+H)^+$: 480.133434. Found: 480.131722.

Example 20

Preparation of N-[2-Bromo-4-(1-methylethyl)phenyl]-N-ethyl-4-(2-carboxyphenyl)-6-methyl-2-pyrimidineamine

The product from Example 18 (75 mg) and con. HCl (aq.) (5 mL) were heated at reflux for 18 hours and concentrated to dryness. The crude product was chromatographed on silica gel using ethyl acetate (20%-80%)/hexane and methanol as eluent. The product was recrystallized to give the title compound (12.1 mg), mp 209-210°C. CI-MS $(M+H)^+$, 456.2, 100%.

Example 21

Preparation of N-(2-Bromo-4-methylthiophenyl)-N-ethyl-4-[2-(trifluoromethyl)phenyl]-6-methyl-2-pyrimidineamine

The product from Example 15 (450 mg), dimethylsulfoxide (12 mL), tetrakis(triphenylphosphine)Pd(0) (40 mg), and sodium thiomethoxide (61 mg) were heated at reflux 18 hours. The reaction was cooled, taken up and partitioned between ethyl acetate (100 mL) and water (100 mL). The ethyl acetate was washed with brine, dried over $MgSO_4$, and concentrated to dryness. The crude product was chromatographed on silica gel giving the title compound (90 mg). CI-HRMS calcd. for $C_{21}H_{20}N_3F_3SBr$ $(M+H)^+$: 482.051340. Found: 482.051434.

Example 22

Preparation of N-(2-Bromo-4-methylsulfonylphenyl)-N-ethyl-4-[2-(trifluoromethyl)phenyl]-6-methyl-2-pyrimidineamine

The product from Example 21 (75 mg), 85% m-chloroperoxybenzoic acid (63 mg), and methylene chloride (1 mL) were stirred at room temperature for 18 hours and then quenched with 1M sodium sulfite (aq.) (1mL). The mixture was partitioned between methylene chloride (10 mL) and sat. sodium bicarbonate (aq.) (10 mL) and the organic layer was concentrated to dryness. The crude product was chromatographed on silica gel using ethyl acetate/hexane (1:1) as eluent to afford the title compound (60 mg). CI-HRMS calcd. for $C_{21}H_{20}N_3O_2F_3SBr$ $(M+H)^+$: 514.041170. Found: 514.043197.

Example 23

Preparation of N-(2-Bromo-4,6-dimethoxyphenyl)-N-ethyl-4-(2-methoxyphenyl)-6-methyl-2-pyrimidineamine

Part A: Anisole (2.16 g), n-butyllithium (2.5 M in hexanes, 4.0 mL), and dry ether (4.0 mL) were stirred 18 h at room temperature. Ether (5 mL) and tetrahydrofuran (5mL) were added to make a 0.47 M solution of 2-methoxyphenyllithium (21.12 mL), of which 0.47 mL was added to 2-chloro-4-methylpyrimidine (0.71 g, prepared as described by Strekowski et al (J. Heterocylic Chem. 27, 1393 (1990)) dissolved in dry ether (37 mL) and stirred 30 minutes at -30°C and 2 hours at 0°C. The reaction was quenched with acetic acid (515 µL), water (36 µL) and tetrahydrofuran (5 mL). 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (1.31 g) dissolved in tetrahydrofuran (5 mL) was added to the reaction which was then stirred 20 minutes. 1N Sodium hydroxide (aq.) (10 mL) was added at 0°C and the

reaction was washed with 1N sodium hydroxide (3 X 10 mL). The organic layer was filtered through silica gel and concentrated to dryness to give 2-chloro-6-methyl-4-(2-methoxyphenyl)pyrimidine (0.72 g).

Part B: . To 2-bromo-4,6-dimethoxyaniline (348 mg) dissolved in toluene (5 mL) was added sodium hydride (180 mg, 60% in oil). The reaction was stirred for 5 minutes at room temperature and the product of part A (352 mg) was added and heated at reflux 4 hours. The reaction was cooled to room temperature and water (20 mL) was slowly added. The mixture was extracted with ethyl acetate (40 mL) which was dried and concentrated to a brown oil (538 mg). The crude product was chromatographed on silica gel using ethyl acetate/hexane (3:7) as eluent to afford *N*-(2-Bromo-4,6-dimethoxyphenyl)-4-(2-methoxyphenyl)-6-methyl-2-pyrimidineamine (72 mg).

Part C: The title compound was prepared using the product from part B in a manner similar to the product of part C of Example 1. CI-HRMS calcd. for $C_{22}H_{25}N_3O_3Br$ $(M+H)^+$: 458.107928. Found: 458.107363.

<u>Example 25</u>

Preparation of N-[2-Bromo-4-(1-methylethyl)phenyl]-N-ethyl-4-(2,4,6-trimethylphenyl)-6-methyl-2-pyrimidineamine

Part A: 2-Bromomesitylene (1.49 g), dry ether (45 mL), and t-butyllithium (1.5 M, 9 mL) were stirred at -78°C for 10 minutes and 2-chloro-4-methylpyrimidine (643 mg) dissolved in dry ether (10 mL) was added. The reaction was stirred at -30°C for 1.5 hours and quenched with a mixture of acetic acid (386 µL), water (23 µL), and tetrahydrofuran (5 mL). 2,3-Dichloro-5,6-dicyano-

1,4-benzoquinone (1.25 g) dissolved in tetrahydrofuran (10 mL) was added to the reaction which was then stirred 15 minutes and washed with 1 N sodium hydroxide (three 50 mL portions), dried, and concentrated. The crude product was chromatographed on silica gel using ethyl acetate/hexane (1:9) as eluent affording 2-chloro-6-methyl-4-(2,4,6-trimethylphenyl)pyrimidine (0.99 g) as a white solid.

Part B: The product from part A (740 mg), 2-bromo-4-isopropylaniline (707 mg) and ethylene glycol (4 mL) were heated at reflux for 1 hour and taken up in ethyl acetate (30 mL) and water (30 mL). The layers were separated and the ethyl acetate was washed with 1 N sodium hydroxide (aq.) (two 20 mL portions), dried and concentrated. The crude product was chromatographed on silica gel using ethyl acetate/hexane (1:9) as eluent affording *N*-[2-Bromo-4-(1-methylethyl)phenyl]-4-(2,4,6-trimethylphenyl)-6-methyl-2-pyrimidineamine (550 mg).

Part C: The title compound was prepared using the product of part B in a manner similar to the product of part C of Example 1. Elemental analysis calcd. for $C_{25}H_{30}N_3Br$: C, 66.37; H, 6.68; N, 9.297. Found: C, 66.39; H, 6.64; N, 9.19.

Example 26

Preparation of N-(2,4-Dibromophenyl)-N-ethyl-4-(2-methylthiophenyl)-6-methyl-2-pyrimidineamine

The title compound was prepared in a manner similar to the product of Example 25. CI-HRMS calcd. for $C_{20}H_{20}N_3SBr$ $(M+H)^+$: 491.974467. Found: 491.974770.

Example 27

Preparation of N-(2,4-Dibromophenyl)-N-ethyl-4-(2-methylsulfonylphenyl)-6-methyl-2-pyrimidineamine

The product of Example 26 (740 mg), m-chloroperoxybenzoic acid (85%, 609 mg), and methylene chloride (10 mL) were stirred at room temperature for 18 hours and then quenched with 1M sodium sulfite (aq.) (5mL). The mixture was partitioned between methylene chloride (40 mL) and sat. sodium bicarbonate (aq.) (40 mL) and the organic layer was concentrated to dryness. The crude product was chromatographed on silica gel using ethyl acetate/hexane (1:1) as eluent to afford the title compound (473 mg). CI-HRMS calcd. for $C_{20}H_{20}N_3O_2SBr$ $(M+H)^+$: 523.964296. Found: 523.966054.

Example 28

Preparation of N-(2-Bromo-4-(1-methylethyl)phenyl)-N-ethyl-4-(2,4-dichlorophenyl)-6-methyl-1,3,5-triazine-2-amine

Part A: Methyl magnesium bromide (300 mmole, 3M in ether, Aldrich) was added dropwise to a solution of cyanic chloride (12.9 g, 69.9 mmole) in CH_2Cl_2 (300 mL) under N_2 at -20°C. Addition was complete in ten minutes. Stirring was continued at -20°C for 4.5 hours. Water (36 mL) was added dropwise while controlling the reaction temperature below -15°C. The reaction mixture was allowed to reach room temperature. Magnesium sulfate (40 g) was added to the reaction mixture and let stand one hour. The reaction mixture was filtered and stripped leaving a yellow solid (11.06 g). This material was purified using flash chromatography (CH_2Cl_2, silica) and gave 2,4-dichloro-6-methyl-1,3,5-triazine as a white solid (7.44g) in 65% yield.

Part B: 2,4-Dichloro-6-methyl-1,3,5-triazine (3 g, 18.29 mmol), 2-bromo-*N*-ethyl-4-isopropylaniline (6.07 g, 25.07 mmol) and diisopropylethylamine (3.2 g, 25.07

mmol) were dissolved in dioxane (60 mL) under N_2 and refluxed three hours. The solvent was stripped and the residue was purified using flash chromatography (CH_2Cl_2, silica). to provide N-(2-bromo-4-isopropylphenyl)-N-ethyl-4-chloro-6-methyl-1,3,5-triazine-2-amine (4.58 g) as a clear oil in 68% yield.

Part C: A mixture of N-(2-bromo-4-isopropylphenyl)-N-ethyl-4-chloro-6-methyl-1,3,5-triazine-2-amine (370 mg), 2,4-dichlorophenylboronic acid (210 mg) tetrakis(triphenylphoshine)palladium(0) (50 mg), 1M aqueous sodium carbonate (2 mL), ethanol (0.75 mL) and benzene (6 mL) was refluxed for 10 hr.The cooled mixture was diluted with ethyl acetate and the aqueous layer was removed. The organic layer was washed with water and brine, dried, and concentrated *in vacuo*. The crude reaction product was chromatographed on silica gel using ethyl acetate / hexanes (1:9) as eluent. The title compound was obtained as a pure colorless viscous oil (210 mg) that crystallized on standing and trituration with petroleum ether to colorless crystals (82 mg). Elemental Analysis: Calcd. for $C_{21}H_{21}N_4Cl_2Br$: C, 52.52: H, 4.417; N, 11.67. Found: C, 52.79; H, 4.34; N, 11.40.

Example 29

Preparation of N-(2-Bromo-4-(1-methylethyl)phenyl)-N-ethyl-4-(2-(trifluoromethyl)phenyl)-6-methyl-1,3,5-triazine-2-amine

The title compound was prepared in a manner similar to the product of Example 28. CI-HRMS calcd. for $C_{22}H_{23}N_4F_3Br_1$ (M+H): 479.105818. Found: 479.104501.

Example 30

Preparation of N-(4-dimethylamino-2-(trifluoromethyl)phenyl)-N-ethyl-4-(2-(trifluoromethyl)phenyl)-6-methyl-1,3,5-triazine-2-amine

The title compound was prepared in a manner similar to the product of Example 28. Elemental Analysis: Calcd. for $C_{22}H_{21}N_5F_6$: C, 56.29: H, 4.519; N, 14.92. Found: C, 56.14; H, 4.53; N, 14.87.

Example 31

Preparation of 4-(2-(Trifluoromethyl)phenyl)-2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidine

A mixture of 4-chloro-2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidine (425 mg, prepared as described by Y. L. Chen in Patent Application WO94/13676), 2-(trifluoromethyl)phenylboronic acid (310 mg) tetrakis(triphenylphoshine)palladium(0) (50 mg), 1M aqueous sodium carbonate (2 mL), ethanol (0.75 mL) and benzene (6 mL) was refluxed for 6 hr. The cooled mixture was diluted with ethyl acetate and the aqueous layer was removed. The organic layer was washed with 1N aqueous sodium hydroxide, and brine, dried, and concentrated *in vacuo*. The crude reaction product was chromatographed on silica gel using ethyl acetate / hexanes (1:3) as eluent. The title compound was obtained as a glass (300 mg) that crystallized on trituration with ether to give crystals, mp 176.5-177.5°. Elemental Analysis: Calcd. for $C_{22}H_{24}N_3F_3$: C, 70.91: H, 5.71; N, 9.92. Found: C, 70.69; H, 5.72; N, 9.84.

Example 32

Preparation of 6-(2-)-2-methyl-9-(2,4,6-trimethylphenyl)-8-azapurine

Part A: 4,6-Dichloro-2-methyl-5-nitropyrimidine (10 g, 48 mmol) dissolved in DMSO / water (480 ml / 48 ml) followed by addition of 2,4,6-trimethylaniline (7.43 ml, 52.8 mmol) dropwise via syringe over 30 minutes. The reaction was stirred at RT for 18 hours and filtered. The solid was washed with water until the filtrate volume reached 600 ml. A 150 ml aliquot was removed, diluted with 1.5 liters water and 100 ml saturated brine, and extracted with 4 X 100 ml methylene chloride. This procedure was repeated until the remainder of the filtrate had been worked up. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude solid was chromatographed on silica gel (350 g, 97/3 methylene chloride / methanol) to give the desired yellow crystalline product, 10.53 g (76%). ^1H NMR ($CDCl_3$, 300 MHz) δ 12.23 (bs, 1H), 10.60 (s, 1H), 6.95 (s, 2H), 2.34 (2, 3H), 2.33 (s, 3H), 2.16 (s, 6H).

Part B: A solution of the product from Part A (1.50 g) in phosphorous oxychloride (20 mL) was heated at 90° for 35 min. The bulk of the excess phosphorous oxychloride was removed on the rotary evaporator, and the thick oil which remained was stirred vigorously with ice water providing a brown solid (1.29 g) which was used without purification in the next reaction.

Part C: The product from Part B (1.23 g) was dissolved in a mixture of methanol (30 mL) and acetic acid (1.5 mL). To this solution at 0° was added iron powder (0.78 g), the mixture was first allowed to come to room temperature, and then was refluxed for 2.5 hr.

Additional iron powder (0.78 g) and acetic acid (1.5 mL) was added and reflux was continued for another 1.5 hr. The cooled reaction mixture was filtered through a pad of filter-aid, and the filter cake was washed with ethyl acetate. The combined filtrates were concentrated *in vacuo*, and partitioned between ethyl acetate and water, the aqueous layer was extracted three times with ethyl acetate and the combined extracts were dried over sodium sulfate and concentrated in vacuo to a brown solid. Chromatography on silica gel (ethyl acetate/ hexanes 1:1) afforded the intermediate diaminopyrimidine (0.56 g).

Part D: To a 2-phase mixture of the product from Part C (0.56 g) in methylene chloride (10 mL) and 50% aqueous acetic acid (8 mL) was added dropwise, a solution of sodium nitrite (152 mg) in water (1 mL). After vigorous stirring for 30 min, the reaction mixture was poured onto water and extracted twice with methylene chloride. The combined extracts were washed with brine, dried and evaporated to 6-chloro-2-methyl-9-(2,4,6-trimethylphenyl)-8-azapurine (0.50 g) as a tan solid, which was used without purification in the next reaction.

Part E: A mixture of 6-chloro-2-methyl-9-(2,4,6-trimethylphenyl)-8-azapurine (450 mg), 2-methylphenylboronic acid (234 mg), tetrakis(triphenylphoshine)palladium(0) (120 mg), 1M aqueous sodium carbonate (2.6 mL), ethanol (1.2 mL) and benzene (8 mL) was refluxed for 2 hr. An additional 50 mg of tetrakis(triphenylphoshine)palladium(0) was added, and the mixture was refluxed overnight. The cooled mixture was diluted with ethyl acetate and the aqueous layer was removed. The organic layer was washed with water and brine, dried, and concentrated *in vacuo*. The crude reaction product was chromatographed on silica gel

using first methylene chloride, then 2% methanol in methylene chloride as eluents. The title compound was obtained as a yellow solid (364 mg) that was recrystallized from ether / petroleum ether (215 mg), mp 140.5 - 141.7°. Elemental Analysis: Calcd. for $C_{21}H_{21}N_5$: C, 73.44: H, 6.16; N, 20.39. Found: C, 73.23; H, 6.22; N, 20.35.

Example 33

Preparation of 6-(2,4-dichlorophenyl)-2-methyl-9-(2,4,6-trimethylphenyl)-8-azapurine

The title compound was prepared in a manner similar to the product of Example 32; mp 166.8-168.2°. Elemental Analysis: Calcd. for $C_{20}H_{17}N_5Cl_2$: C, 60.31: H, 4.30; N, 17.58. Found: C, 59.75; H, 4.40; N, 17.33.

Example 34

Preparation of 6-(2-methylphenyl)-2-methyl-9-(2-chloro-4,6-dimethoxyphenyl)-8-azapurine

The title compound was prepared in a manner similar to the product of Example 32; mp 172.9-173.8°. Elemental Analysis: Calcd. for $C_{20}H_{18}N_5O_2Cl$: C, 60.68: H, 4.58; N, 17.69. Found: C, 60.18; H, 4.54; N, 17.38.

Example 35

Preparation of 6-(2-(trifluoromethyl)phenyl)-2-methyl-9-(2,4,6-trimethylphenyl)-8-azapurine

The title compound was prepared in a manner similar to the product of Example 32; mp 138.6-139.3°. Elemental Analysis: Calcd. for $C_{21}H_{18}N_5F_3$: C, 63.47:

H, 4.51; N, 17.62. Found: C, 63.41; H, 4.51; N, 17.64.

Example 36

Preparation of 9-(2-Bromo-4,6-dimethoxyphenyl)-7,9-dihydro-2-methyl-6-(2-(trifluoromethyl)phenyl)-8H-purin-8-one

Part A: To a solution of 4,6-dichloro-2-methyl-5-nitropyrimidine (3.12 g, 15 mmol, J. Chem. Soc 3832 (1954); *ibid* 677 (1944)) and 2-(trifluoromethyl)phenylboronic acid (3.42 g, 18 mmol) in benzene (50 ml) was added 1M aqueous sodium carbonate (20 ml) and 500 mg of tetrakis(triphenylphosphine)palladium. This mixture was refluxed for 4.5 hours, then was diluted with ethyl acetate, washed with water and brine, dried over sodium sulfate, filtered, and concentrated *in vacuo.* Chromatography on silica gel (10% then 20% ethylacetate in hexanes) afforded 4-Chloro-2-methyl-5-nitro-6-(2-(trifluoromethyl)phenyl)-pyrimidine (1.90 g) as a pale yellow solid. CI Mass Spec. $(M+H)^+$ = 318.0.

Part B: The product from Part A (2.89 g), 2-bromo-4,6-dimethoxyaniline (2.59 g), and diisopropylethylamine (1.89 ml) in dioxane (90 ml) was refluxed overnight. The cooled solution was poured onto water and extracted 2 times with ethyl acetate. The combined extracts were washed with saturated aqueous sodium chloride, dried over sodium sulfate, filtered, and concentrated *in vacuo*. The dark-colored oil was chromatographed on silica gel (10% to 50% ethyl acetate in hexanes) affording 4.5 g of an orange amorphous solid. Recrystallization from ethyl acetate / ether / petroleum ether afforded 3.08 g of 4-(2-Bromo-4,6-dimethoxyphenyl)amino-2-methyl-5-nitro-6-(2-

(trifluoromethyl)phenyl)pyrimidine as an orange solid, mp 146.8-147.8°. Elemental Analysis: Calcd. for $C_{20}H_{16}N_4O_4F_3Br_1$: C, 46.80: H, 3.14; N, 10.92. Found: C, 46.76; H, 3.15; N, 10.76.

Part C: A mixture of the product from Part B (2.84 g), iron filings (5 g), acetic acid (7 ml), and methanol (100 ml) was brought to reflux. When no reaction was observed to occur by tlc, a small amount of HCl treated iron filings were added to the reaction mixture. After 2.5 hours at reflux, the cooled reaction mixture was filteed through filter-aid. The filter pad was washed with methanol and methylene chloride, and the combined filtrates were concentrated *in vacuo*. The crude product was partitioned between ethyl acetate and water, the aqueous layer was reextracted with ethyl acetate and the combined extracts were washed with saturated aqueous sodium chloride, dried over sodium sulfate, filtered, and concentrated *in vacuo*. The orange solid was redissolved in ethyl acetate, and this solution was washed twice with aqueous sodium bicarbonate and concentrated *in vacuo* to afford 1.84 g of an orange solid, 5-Amino-4-(2-bromo-4,6-dimethoxyphenyl)amino-2-methyl-6-(2-(trifluoromethyl)phenyl)-pyrimidine, which was used without purification in Part D. A portion of this material was recrystallized from ethyl acatete/hexanes to afford a white solid. CI Mass Spec. $(M+H)^+$ = 483.1.

Part D: A mixture of the product from Part C (250 mg), phosgene (2.7 ml of a 1.93M solution in toluene), and in dry toluene (6 ml) was refluxed for 30 minutes. The cooled mixture was poured onto water and extracted 3 times with ethyl acetate. The combined extracts were dried over sodium sulfate, filtered, and concentrated *in vacuo* . The crude product was purified

by preparative TLC on silica gel (3/1 ethyl acetate / hexanes) to afford the title compound (128 mg) as a solid, mp 255-256°. CI-HRMS calcd. for $C_{21}H_{17}N_4O_3F_3Br_1$ (M+H): 509.044. Found: 509.044742.

Example 37

Preparation of 9-(2-Bromo-4,6-dimethoxyphenyl)-7,9-dihydro-2,7-dimethyl-6-(2-trifluoromethyl)phenyl)-8H-purin-8-one:

To a solution of the product from Example 36, Part D (107 mg) in acetone (5 ml) was added powdered potasium hydroxide (24 mg) and methyl iodide (0.027 ml). The reaction mixture was stirred at room temperature for 2 hours, then concentrated *in vacuo*. The crude product was taken up in a mixture of water (15 ml) and saturated sodium chloride (5 ml) which was extracted 3 times with ethyl acetate. The combined extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. to an oil which crystallized from ether. Recrystallization from ether afforded the title compound (74 mg) as a white crystalline solid, mp 199-200°. Elemental Analysis: Calcd. for $C_{22}H_{18}N_4O_3F_3Br_1$: C, 50.49: H, 3.477; N, 10.71. Found: C, 50.81; H, 3.58; N, 10.34.

Example 38

Preparation of 9-(2-Bromo-4,6-dimethoxyphenyl)-2,8-dimethyl-6-(2-trifluoromethyl)phenyl)purine

To a solution of the product from Example 36, Part C (200 mg) in methylene chloride (4 mL) was added 4M hydrogen chloride in dioxane (0.5 mL) and triethylorthoacetate (4 mL). The reaction mixture was stirred for 1.5 hr at room temperature and then was

poured onto saturated sodium bicarbonate. This mixture was extracted twice with methylene chloride, and the combined extracts were dried over sodium sulfate and concentrated *in vacuo*.to a tan solid.

This material was combined with xylenes (20 mL) and refluxed overnight. The cooled mixture was concentrated *in vacuo*, and the crude reaction product was chromatographed on silica gel using first 50% then 70% ethyl acetate in hexanes. Two recrystallizations from ether afforded the title compound as colorless crystals (70 mg), mp 149-150°. Elemental Analysis: Calcd. for $C_{22}H_{18}N_4F_3BrO_2$: C, 52.09: H, 3.586; N, 11.04. Found: C, 51.78; H, 3.64; N, 10.94.

Example 39

Preparation of 9-(2-Bromo-4,6-dimethoxyphenyl)-2-methyl-6-(2-trifluoromethyl)phenyl)-8-azapurine

To a solution of the product from Example 36, Part C (250 mg) in methylene chloride (10 mL) and 50% aqueous acetic acid (4 mL) was added dropwise, a solution of sodium nitrite (40 mg) in water (0.5 mL). The mixture was stirred at room temperature for 30 min and poured onto water. This was extracted twice with metylene chloride, and the combied extracts were washed with brine, dried and concentrated *in vacuo* to an orange solid (235 mg). Recrystallization first from ether, and then from ethyl acetate - hexane afforded a colorless solid (130 mg), mp 157.8-158.3°. Elemental Analysis: Calcd. for $C_{20}H_{15}N_5F_3BrO_2$: C, 48.60: H, 3.069; N, 14.17. Found: C, 48.77; H, 3.15; N, 13.98.

Example 40

Preparation of 9-(2-Bromo-4,-isopropylphenyl)-2-methyl-6-(2-trifluoromethyl)phenyl)-8-azapurine

The title compound was prepared in a manner similar to the product of Example 39; mp 152.2-153.2°. Elemental Analysis: Calcd. for $C_{21}H_{17}BrF_3$: C, 52.96: H, 3.607; N, 14.70. Found: C, 52.95; H, 3.52; N, 14.65.

Example 41

Preparation of 9-(2-Bromo-4-isopropylphenyl)-7,9-dihydro-2,7-dimethyl-6-(2-trifluoromethyl)phenyl)-8H-purin-8-one

Part A: The product from Example 36, Part A (1.9 g) and 2-bromo-4-isopropylaniline (1.5 g) in tetrahydrofuran (20 ml) was refluxed for 5 hours. The cooled solution was diluted with ethyl acetate, washed with dilute aqueous sodium bicarbonate and saturated aqueous sodium chloride, dried over sodium sulfate, filtered, and concentrated *in vacuo*. Trituration with a mixture of ether and petroleum ether afforded the desired product (2.63 g) as orange crystals which were used directly in Part B. A portion of this material was recrystallized from isopropanol giving 4-(2-bromo-4-isopropylphenyl)amino-2-methyl-5-nitro-6-(2-(trifluoromethyl)phenyl)pyrimidine as orange-yellow crystals, mp 145.5-146.5°. Elemental Analysis: Calcd. for $C_{21}H_{18}N_4O_2F_3Br_1$: C, 50.92: H, 3.66; N, 11.31. Found: C, 50.91; H, 3.55; N, 11.10.

Part B: To a solution of the product from Part A (1.0 g) in dioxane (50 ml) was added in succession: water (50 ml), concentrated aqueous ammonia (3 ml), and sodium dithionite (2.78 g). After stirring 30 minutes at room temperature, the reaction mixture was poured onto water and extracted three times with ethyl acetate. The combined extracts were washed with brine, dried, and

concentrated *in vacuo*. The crude oil was chromatographed on silica gel (25% then 50% ethyl acetate in hexanes) to afford 5-amino-4-(2-bromo-4-isopropylphenyl)amino-2-methyl-6-(2-(trifluoromethyl)phenyl)-pyrimidine as an off-white solid (350 mg). ^{1}HNMR ($CDCl_3$), 300 MHz) δ 8.57 (d, 1H, J = 8.8 Hz), 7.82 (d, 1H, J = 7.7 Hz), 7.63 (m, 3H), 7.42 (m, 2H), 7.24 (m, 1H), 2.87 (m, 1H), 2.83 (bs, 2H), 2.59 (s, 3H), 1.26 (d, 6H, J = 7.0 Hz).

Part C: A mixture of the product from Part B (200 mg), phosgene (2.2 ml of a 1.93M solution in toluene), and in dry toluene (6 ml) was refluxed for 2 hours. The cooled mixture was poured onto water and extracted 3 times with ethyl acetate. The combined extracts were dried over sodium sulfate, filtered, and concentrated *in vacuo* to 9-(2-bromo-4-isopropylphenyl)-7,9-dihydro-2-methyl-6-(2-trifluoromethyl)phenyl)-8H-purin-8-one (250 mg) as an off-white solid which was used without purification in Part D. ^{1}HNMR ($CDCl_3$), 300 MHz) δ 8.17 (bs, 1H), 7.83 (d, 1H, J = 7.0 Hz), 7.15-7.7 (m, 6H), 3.00 (m, 1H), 2.67 (s, 3H), 1.32 (d, 6H, J = 6.5 Hz).

Part D: To a solution of the product from Part C (174 mg) in acetone (5 ml) was added powdered potasium hydroxide (39 mg) and methyl iodide (0.044 ml). The reaction mixture was stirred at room temperature for 3 hours, then concentrated *in vacuo*. The crude product was taken up in a mixture of water (20 ml) and saturated sodium chloride (5 ml) which was extracted 3 times with ethyl acetate. The combined extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. the white solid product was chromatographed on silica gel (33% then 50% ethyl acetate in hexanes) affording 158 mg of a solid which was recrystallized from ether/petroleum ether to give 103 mg of the title compound as white

crystalline solid, mp 163-164°. Elemental Analysis: Calcd. for $C_{23}H_{20}N_4O_1F_3Br_1$: C, 54.67: H, 3.99; N, 11.09. Found: C, 54.71; H, 4.09; N, 10.97.

Preparation A
2-(Trifluoromethyl)phenylboronic acid

To a stirred solution of 2-Bromo-(trifluoromethyl)benzene (18.2 mL, 0.133 moles) in dry THF (150 mL) at -78° was added dropwise over a 25 min period n-butyllithium (60 mL of 2.5M in hexanes, 0.147 moles). The solution was stirred at -78° for 1 hour, and then a solution of triisopropyborate (37 mL) in THF (50 mL) was added dropwise over 30 min at -78°. The cooling bath was removed and the reaction mixture was stirred at ambient temperature overnight. The solution was then cooled to 0°, and made acidic with 1N aqueous hydrochloric acid. The resulting mixture was extracted twice with ether, and the combined extracts were extracted twice with 1N sodium hydroxide. The combined aqueous extracts were acidified to pH 2 with 1N hydrochloric acid and extracted twice with ether. The combined extracts were dried over magnesium chloride, and concentrated in vacuo to a white solid (20.95 g). Two recrystallizations from water afforded the title compound as a colorless solid (11.35 g).

Utility

CRF-R1 Receptor Binding Assay for the Evaluation of Biological Activity

The following is a description of the isolation of cell membranes containing cloned human CRF-

R1 receptors for use in the standard binding assay as well as a description of the assay itself.

Messenger RNA was isolated from human hippocampus. The mRNA was reverse transcribed using oligo (dt) 12-18 and the coding region was amplified by PCR from start to stop codons The resulting PCR fragment was cloned into the EcoRV site of pGEMV, from whence the insert was reclaimed using XhoI + XbaI and cloned into the XhoI + XbaI sites of vector pm3ar (which contains a CMV promoter, the SV40 't' splice and early poly A signals, an Epstein-Barr viral origin of replication, and a hygromycin selectable marker). The resulting expression vector, called phchCRFR was transfected in 293EBNA cells and cells retaining the episome were selected in the presence of 400 mM hygromycin. Cells surviving 4 weeks of selection in hygromycin were pooled, adapted to growth in suspension and used to generate membranes for the binding assay described below. Individual aliquots containing approximately 1 x 10^8 of the suspended cells were then centrifuged to form a pellet and frozen.

For the binding assay a frozen pellet described above containing 293EBNA cells transfected with hCRFR1 receptors is homogenized in 10 ml of ice cold tissue buffer (50 mM HEPES buffer pH 7.0, containing 10 mM $MgCl_2$, 2 mM EGTA, 1 mg/l aprotinin, 1 mg/ml leupeptin and 1 mg/ml pepstatin). The homogenate is centrifuged at 40,000 x g for 12 min and the resulting pellet rehomogenized in 10 ml of tissue buffer. After another centrifugation at 40,000 x g for 12 min, the pellet is resuspended to a protein concentration of 360 mg/ml to be used in the assay.

Binding assays are performed in 96 well plates; each well having a 300 ml capacity. To each well is added 50 ml of test drug dilutions (final concentration of drugs range from 10^{-10} - 10^{-5} M), 100 ml of ^{125}I-ovine-CRF (^{125}I-o-CRF) (final concentration 150 pM) and 150 ml of the cell homogenate described above. Plates

are then allowed to incubate at room temperature for 2 hours before filtering the incubate over GF/F filters (presoaked with 0.3% polyethyleneimine) using an appropriate cell harvester. Filters are rinsed 2 times with ice cold assay buffer before removing individual filters and assessing them for radioactivity on a gamma counter.

Curves of the inhibition of ^{125}I-o-CRF binding to cell membranes at various dilutions of test drug are analyzed by the iterative curve fitting program LIGAND [P.J. Munson and D. Rodbard, *Anal. Biochem.* 107:220 (**1980**), which provides Ki values for inhibition which are then used to assess biological activity.

A compound is considered to be active if it has a K_i value of less than about 10000 nM for the inhibition of CRF.

Inhibition of CRF-Stimulated Adenylate Cyclase Activity

Inhibition of CRF-stimulated adenylate cyclase activity was performed as described by G. Battaglia et al. *Synapse* **1**:572 (**1987**). Briefly, assays were carried out at 37° C for 10 min in 200 ml of buffer containing 100 mM Tris-HCl (pH 7.4 at 37° C), 10 mM $MgCl_2$, 0.4 mM EGTA, 0.1% BSA, 1 mM isobutylmethylxanthine (IBMX), 250 units/ml phosphocreatine kinase, 5 mM creatine phosphate, 100 mM guanosine 5'-triphosphate, 100 nM oCRF, antagonist peptides (concentration range 10^{-9} to 10^{-6m}) and 0.8 mg original wet weight tissue (approximately 40-60 mg protein). Reactions were initiated by the addition of 1 mM ATP/^{32}P]ATP (approximately 2-4 mCi/tube) and terminated by the addition of 100 ml of 50 mM Tris-HCL, 45 mM ATP and 2% sodium dodecyl sulfate. In order to monitor the recovery of cAMP, 1 µl of [^{3}H]cAMP (approximately 40,000 dpm) was added to each tube prior to separation. The separation of [^{32}P]cAMP

from [^{32}P]ATP was performed by sequential elution over Dowex and alumina columns. Recovery was consistently greater than 80%.

Some compounds of this invention were tested in this assay and found to be active.

In vivo Biological Assay

The *in vivo* activity of the compounds of the present invention can be assessed using any one of the biological assays available and accepted within the art. Illustrative of these tests include the Acoustic Startle Assay, the Stair Climbing Test, and the Chronic Administration Assay. These and other models useful for the testing of compounds of the present invention have been outlined in C.W. Berridge and A.J. Dunn *Brain Research Reviews* 15:71 (**1990**)

Compounds may be tested in any species of rodent or small mammal. Disclosure of the assays herein is not intended to limit the enablement of the invention.

Compounds of this invention have utility in the treatment of abnormalities in humans and other mammals which are associated with corticotropin releasing factor and/or a receptor for corticotropin releasing factor. This includes depression, affective disorders, anxiety, irritable bowel syndrome, post-traumatic stress disorder, supranuclear palsy, epilepsy, seizures, immune suppression, Alzheimer's disease, gastrointestinal disease, anorexia nervosa or other feeding disorder, drug or alcohol withdrawal symptoms, drug addiction, inflammatory disorders, fertility problems. It includes numerous other disorders such as those mentioned in the disclosure of Pfizer WO95/33750, at pages 7 and 8, which is incorporated herein by reference.

Compounds of this invention can be administered to treat these abnormalities by means that produce contact of the active agent with the agent's site of action in the body of a mammal. The compounds can be administered by any conventional means available for use in conjunction with pharmaceuticals either as individual therapeutic agent or in combination of therapeutic agents. They can be administered alone, but will generally be administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

The dosage administered will vary depending on the use and known factors such as pharmacodynamic character of the particular agent, and its mode and route of administration; the recipient's age, weight, and health; nature and extent of symptoms; kind of concurrent treatment; frequency of treatment; and desired effect. For use in the treatment of said diseases or conditions, the compounds of this invention can be orally administered daily at a dosage of the active ingredient of 0.002 to 200 mg/kg of body weight. Ordinarily, a dose of 0.01 to 10 mg/kg in divided doses one to four times a day, or in sustained release formulation will be effective in obtaining the desired pharmacological effect.

Dosage forms (compositions) suitable for administration contain from about 1 mg to about 100 mg of active ingredient per unit. In these pharmaceutical compositions, the active ingredient will ordinarily be present in an amount of about 0.5 to 95% by weight based on the total weight of the composition.

The active ingredient can be administered orally is solid dosage forms, such as capsules, tablets and powders; or in liquid forms such as elixirs, syrups,

and/or suspensions. The compounds of this invention can also be administered parenterally in sterile liquid dose formulations.

Gelatin capsules can be used to contain the active ingredient and a suitable carrier such as but not limited to lactose, starch, magnesium stearate, steric acid, or cellulose derivatives. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as sustained release products to provide for continuous release of medication over a period of time. Compressed tablets can be sugar-coated or film-coated to mask any unpleasant taste, or used to protect the active ingredients from the atmosphere, or to allow selective disintegration of the tablet in the gastrointestinal tract.

Liquid dose forms for oral administration can contain coloring or flavoring agents to increase patient acceptance.

In general, water, pharmaceutically acceptable oils, saline, aqueous dextrose (glucose), and related sugar solutions and glycols, such as propylene glycol or polyethylene glycol, are suitable carriers for parenteral solutions. Solutions for parenteral administration preferably contain a water soluble salt of the active ingredient, suitable stabilizing agents, and if necessary, butter substances. Antioxidizing agents, such as sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or in combination, are suitable stabilizing agents. Also used are citric acid and its salts, and EDTA. In addition, parenteral solutions can contain preservatives such as benzalkonium chloride, methyl- or propyl-paraben, and chlorobutanol.

Suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences", A. Osol, a standard reference in the field.

Useful pharmaceutical dosage-forms for administration of the compounds of this invention can be illustrated as follows:

Capsules

A large number of units capsules are prepared by filling standard two-piece hard gelatin capsules each with 100 mg of powdered active ingredient, 150 mg lactose, 50 mg cellulose, and 6 mg magnesium stearate.

Soft Gelatin Capsules

A mixture of active ingredient in a digestible oil such as soybean, cottonseed oil, or olive oil is prepared and injected by means of a positive displacement was pumped into gelatin to form soft gelatin capsules containing 100 mg of the active ingredient. The capsules were washed and dried.

Tablets

A large number of tablets are prepared by conventional procedures so that the dosage unit was 100 mg active ingredient, 0.2 mg of colloidal silicon dioxide, 5 mg of magnesium stearate, 275 mg of microcrystalline cellulose, 11 mg of starch, and 98.8 mg lactose. Appropriate coatings may be applied to increase palatability or delayed adsorption.

The compounds of this invention may also be used as reagents or standards in the biochemical study of neurological function, dysfunction, and disease and immunological or cardiovascular disease.

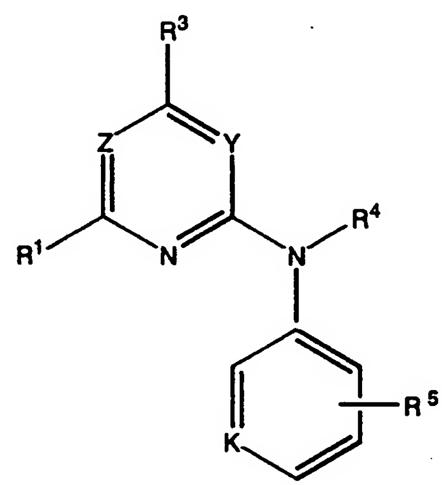
Although the present invention has been described and exemplified in terms of certain preferred embodiments, other embodiments will be apparent to those skilled in the art. The invention is, therefore, not limited to the particular

embodiments described and exemplified, but is capable of modification or variation without departing from the spirit of the invention, the full scope of which is delineated by the appended claims.

CLAIMS

WHAT IS CLAIMED IS:

1. A method of treating affective disorder, anxiety, depression, headache, irritable bowel syndrome, post-traumatic stress disorder, supranuclear palsy, immune suppression, Alzheimer's disease, gastrointestinal diseases, anorexia nervosa or other feeding disorder, drug addiction, drug or alcohol withdrawal symptoms, inflammatory diseases, cardiovascular or heart-related diseases, fertility problems, human immunodeficiency virus infections, hemorrhagic stress, obesity, infertility, head and spinal cord traumas, epilepsy, stroke, ulcers, amyotrophic lateral sclerosis, hypoglycemia or a disorder the treatment of which can be effected or facilitated by antagonizing CRF, including but not limited to disorders induced or facilitated by CRF, in mammals, comprising: administering to the mammal a therapeutically effective amount of a compound of formula (I):



(I)

or a stereoisomer or pharmaceutically acceptable salt form thereof, wherein:

Y is CR^2 or N;

Z is CH or N;

K is CR^5 or N;

R^1 is C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, chloro, fluoro, cyano, or trifluoromethyl;

R^2 taken together with R^4 is -E-F-, where E and F are independently CR^9 and CR^{9a}; or R^2 taken together with R^4 is -A=D-, where A and D are each independently CH, CR^{10} or N; provided that -A=D- may not be -CH=N- or CR^{10}=N- oriented in such a way as to form a pyrazole ring, but may be -CH=N- or CR^{10}=N- oriented in such a way as to form an imidazole ring; or R^2 taken together with R^4 is -A-D- where A is NR^9 and D is C=O oriented in such a way as to form an imidazolone.

R^3 is phenyl substituted on 1-4 ring carbons with R^8, napthyl substituted on 1-4 ring carbons with R^8, pyridinyl substituted on 1-4 ring carbons with R^8, or pyrimidinyl substituted on 1-3 ring carbons with R^8;

R^4 is C_1-C_4 alkyl, allyl, or propargyl, where C_1-C_4 alkyl is optionally substituted with C_3-C_6 cycloalkyl, OH, $-OR^9$, $-S(O)_nR^9$ or $-CO_2R^9$;

R^5 represents 1-4 substituents on ring carbons each of which may be independently C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_6

cycloalkyl, C_4-C_{10} cycloalkylalkyl, halo, nitro,cyano, $-NR^6R^7$, $-OR^7$, $-COR^7$, $-C(O)NR^6R^7$, $-C(NOR^9)R^7$, or $-S(O)_nR^7$, where C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_6 cycloalkyl and C_4-C_{10} cycloalkylalkyl are optionally substituted with 1 to 3 substituents independently selected from halo, nitro, cyano, $-NR^6R^7$, $-OR^7$, $-COR^7$, $-C(O)NR^6R^7$, $-S(O)_nR^7$, and $-C(NOR^9)R^7$ and two R^5 moieties taken together may comprise $CR^9R^{9a}CR^9R^{9a}O$, $CR^9R^{9a}CR^9R^{9a}CR^9R^{9a}$, or $CR^9{=}CR^{9a}O$;

R^6 and R7 are independently at each occurrence H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, $-(CH_2)_m$-phenyl, or $-(CH_2)_m$-heteroaryl; all optionally substituted with 1-3 R^{11}'s.

R^8 is independently at each occurrence C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_4-C_{10} cycloalkylalkyl, phenyl, heteroaryl, halo, nitro,cyano, $-NR^6R^7$, $-OR^7$, $-COR^7$, $-CO_2R^7$, $-C(O)NR^6R^7$, $-OC(O)NR^6R^7$, $-NR^9C(O)NR^6R^7$, $-NR^6C(O)R^7$, $-C(NOR^9)R^7$, $-S(O)_nR^7$, $-NR^9SO_2R^7$, $-SO_2NR^6R^7$, and where C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_4-C_{10} cycloalkylalkyl, and phenyl are optionally substituted with 1 to 3 substituents independently selected from halo, nitro, cyano, $-NR^6R^7$, $-OR^7$, $-COR^7$, $-C(O)NR^6R^7$, $-S(O)_nR^7$, $-C(NOR^9)R^7$, $-NR^9SO_2R^7$, and $-SO_2NR^6R^7$; provided that when R^3 is pyridinyl, at least one R^8 is other than methyl; further provided that when R^3 is phenyl, at least one R^8 is other than unsubstituted phenyl;

R^9 and R^{9a} is H or C_1-C_4 alkyl;

R^{10} is C_1-C_4 alkyl, halo, nitro, cyano, $-NR^9R^{9a}$, $-OR^{12}$, or $-S(O)_nR^{12}$;

R^{11} is independently at each occurrence C_1-C_3 alkyl, halo, nitro, cyano, $-NR^9R^{9a}$, $-OR^9$ $-S(O)_nR^{12}$, $-COR^9$, $-CO_2R^9$, $-C(O)NR^9R^{9a}$, $-NR^9C(O)R^{9a}$, or $-C(NOR^9)R^{9a}$.

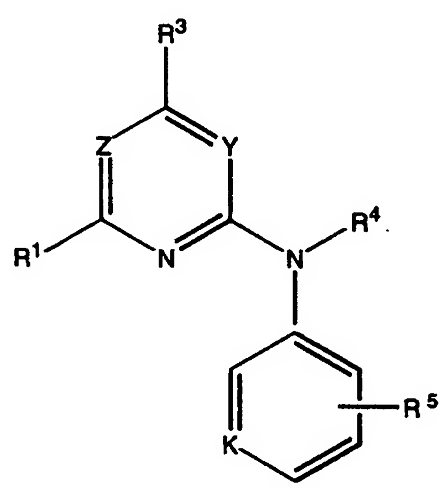
R^{12} is C_1-C_4 alkyl;

heteroaryl is pyridyl, pyrimidinyl, triazinyl, furanyl, quinolinyl, isoquinolinyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrrolyl, oxazolyl, benzofuranyl, benzothienyl, benzthiazolyl, isoxazolyl, pyrazolyl, triazolyl, tetrazolyl, indazolyl, 2,3-dihydrobenzofuranyl or 2,3-dihydrobenzothienyl;

n is independently at each occurrence 0, 1 or 2; and

m is independently at each occurrence 0-6.

2. A compound of formula I:



(I)

or a pharmaceutically acceptable salt or pro-drug form thereof, wherein:

Y is CR^2 or N;

Z is CH or N;

K is CR^5 or N;

R^1 is C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, chloro, fluoro, cyano, or trifluoromethyl;

R^2 taken together with R^4 is -E-F-, where E and F are independently CR^9 and CR^{9a}; or R^2 taken together with R^4 is -A=D-, where A and D are each independently CH, CR^{10} or N; provided that -A=D- may not be -CH=N- or CR^{10}=N- oriented in such a way as to form a pyrazole ring, but may be -CH=N- or CR^{10}=N- oriented in such a way as to form an imidazole ring; or R^2 taken together with R^4 is -A-D- where A is NR^9 and D is C=O oriented in such a way as to form an imidazolone.

R^3 is phenyl substituted on 1-4 ring carbons with R^8, napthyl substituted on 1-4 ring carbons with R^8, pyridinyl substituted on 1-4 ring carbons with R^8, or pyrimidinyl substituted on 1-3 ring carbons with R^8;

R^4 is C_1-C_4 alkyl, allyl, or propargyl, where C_1-C_4 alkyl is optionally substituted with C_3-C_6 cycloalkyl, OH, $-OR^9$, $-S(O)_nR^9$ or $-CO_2R^9$;

R^5 represents 1-4 substituents on ring carbons each of which may be independently C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_6 cycloalkyl, C_4-C_{10} cycloalkylalkyl, halo,

nitro,cyano, $-NR^6R^7$, $-OR^7$, $-COR^7$, $-C(O)NR^6R^7$, $-C(NOR^9)R^7$, or $-S(O)_nR^7$, where C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_6 cycloalkyl and C_4-C_{10} cycloalkylalkyl are optionally substituted with 1 to 3 substituents independently selected from halo, nitro, cyano, $-NR^6R^7$, $-OR^7$, $-COR^7$, $-C(O)NR^6R^7$, $-S(O)_nR^7$, and $-C(NOR^9)R^7$ and two R^5 moieties taken together may comprise $CR^9R^{9a}CR^9R^{9a}O$, $CR^9R^{9a}CR^9R^{9a}CR^9R^{9a}$, or $CR^9{=}CR^{9a}O$;

R^6 and R7 are independently at each occurrence H, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, $-(CH_2)_m$-phenyl, or -$(CH_2)_m$-heteroaryl; all optionally substituted with 1-3 R^{11}'s.

R^8 is independently at each occurrence C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_4-C_{10} cycloalkylalkyl, phenyl, heteroaryl, halo, nitro,cyano, $-NR^6R^7$, $-OR^7$, $-COR^7$, $-CO_2R^7$, -$C(O)NR^6R^7$, $-OC(O)NR^6R^7$, $-NR^9C(O)NR^6R^7$, $-NR^6C(O)R^7$, $-C(NOR^9)R^7$, $-S(O)_nR^7$, $-NR^9SO_2R^7$, $-SO_2NR^6R^7$, and where C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_4-C_{10} cycloalkylalkyl, and phenyl are optionally substituted with 1 to 3 substituents independently selected from halo, nitro, cyano, $-NR^6R^7$, $-OR^7$, $-COR^7$, $-C(O)NR^6R^7$, -$S(O)_nR^7$, $-C(NOR^9)R^7$, $-NR^9SO_2R^7$, and $-SO_2NR^6R^7$; provided that when R^3 is pyridinyl, at least one R^8 is other than methyl; further provided that when R^3 is phenyl, at least one R^8 is other than unsubstituted phenyl;

R^9 and R^{9a} is H or C_1-C_4 alkyl;

R^{10} is C_1-C_4 alkyl, halo, nitro, cyano, $-NR^9R^{9a}$, $-OR^{12}$, or $-S(O)_nR^{12}$;

R^{11} is independently at each occurrence C_1-C_3 alkyl, halo, nitro, cyano, $-NR^9R^{9a}$, $-OR^9$ $-S(O)_nR^{12}$, $-COR^9$, $-CO_2R^9$, $-C(O)NR^9R^{9a}$, $-NR^9C(O)R^{9a}$, or $-C(NOR^9)R^{9a}$.

R^{12} is C_1-C_4 alkyl;

heteroaryl is pyridyl, pyrimidinyl, triazinyl, furanyl, quinolinyl, isoquinolinyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrrolyl, oxazolyl, benzofuranyl, benzothienyl, benzthiazolyl, isoxazolyl, pyrazolyl, triazolyl, tetrazolyl, indazolyl, 2,3-dihydrobenzofuranyl or 2,3-dihydrobenzothienyl;

n is independently at each occurrence 0, 1 or 2; and

m is independently at each occurrence 0-6;

with the provisos that:

(1) when R^4 is C_1-C_4 alkyl and Y is N, then Z is N;

(2) when R^3 is phenyl, Y is N, and Z is CH, at least one R^8 is other than dimethylamino or -$NCH_3C(O)CH_3$;

(3) when Z and K are CH, R^5 is $-OR^7$, and R^7 is CH_2R^{11}, then R^{11} is not CO_2R9; and

(4) when Y and Z are both N, K is CH, and R^3 is phenyl, then R1 is not chloro or fluoro.

3. A compound of claim 2 or a stereoisomer or pharmaceutically acceptable salt form thereof, wherein:

K is CR^5;

Y is N;

Z is CH or N;

R^1 is methyl;

R^3 is an phenyl moiety substituted with 1-3 substituents independently selected from the group consisting of: halo, methoxy, nitro, trifluoromethyl, methyl, amino, methylamino, dimethylamino, cyano, 4-tetrazolyl, carboxy, methylthio, methylsulfonyl, dichloro;

R^4 is ethyl;

R^5 is selected from the group consisting of C_{1-4} alkyl, C_{1-4} alkoxy, halo, acetyl, dimethylamino, cyano, methylthio, methylsulfonyl.

4. A compound of claim 2 or a stereoisomer or pharmaceutically acceptable salt form thereof, wherein:

K is CR^5;

Y is CR^2;

Z is CH or N;

R^1 is methyl;

R^2 taken together with R^4 is -A=D-, where A and D are each CMe or N oriented in such a way as to form an imidazole or a triazole ring, or A is NR^9 and

D is C=O oriented in such a way as to form an imidazolone;

R^3 is an phenyl moiety substituted with 1-3 substituents independently selected from the group consisting of trifluoromethyl, methyl, chloro; and

R^5 is selected from the group consisting of C_{1-4} alkyl, C_{1-4} alkoxy, halo, acetyl, dimethylamino, cyano, methylthio, methylsulfonyl.

5. A compound of claim 2 selected from the group:

N-(2-Bromo-(1-methylethyl)phenyl)-N-ethyl-4-(2-chlorophenyl)-6-methyl-2-pyrimidineamine;

N-(2-Bromo-4,6-dimethoxyphenyl)-N-ethyl-4-(2-(trifluoromethy)phenyl)-6-methyl-2-pyrimidineamine;

N-(2-Bromo-4-(1-methylethyl)phenyl)-N-ethyl-4-(2-(trifluoromethyl)phenyl)-6-methyl-2-pyrimidineamine;

N-(2-Bromo-4-dimethylamino-6-methoxyphenyl)-N-ethyl-4-(2-(trifluoromethyl)phenyl)-6-methyl-2-pyrimidineamine;

N-(2-Bromo-4-(1-methylethyl))-N-ethyl-4-(3-(trifluoromethyl)phenyl)-6-methyl-2-pyrimidineamine;

N-(2-Bromo-4,6-dimethoxyphenyl)-N-ethyl-4-(2-chlorophenyl)-6-methyl-2-pyrimidineamine;

N-[2-Bromo-4-(1-methylethyl)phenyl]-N-ethyl-4-(2-nitrophenyl)-6-methyl-2-pyrimidineamine;

N-(2,4-Dibromophenyl)-N-ethyl-4-[2-(trifluoromethyl)phenyl]-6-methyl-2-pyrimidineamine;

N-(4-Acetyl-2-bromophenyl)-N-ethyl-4-[2-(trifluoromethyl)phenyl]-6-methyl-2-pyrimidineamine;

N-[2-Bromo-4-(1-methylethyl)phenyl]-N-ethyl-4-(2-cyanophenyl)-6-methyl-2-pyrimidineamine;

N-(2-Bromo-4-methylthiophenyl)-N-ethyl-4-[2-(trifluoromethyl)phenyl]-6-methyl-2-pyrimidineamine;

N-(2-Bromo-4-methylsulfonylphenyl)-N-ethyl-4-[2-(trifluoromethyl)phenyl]-6-methyl-2-pyrimidineamine;

N-[2-Bromo-4-(1-methylethyl)phenyl]-N-ethyl-4-(2,4,6-trimethylphenyl)-6-methyl-2-pyrimidineamine;

N-(2,4-Dibromophenyl)-N-ethyl-4-(2-methylthiophenyl)-6-methyl-2-pyrimidineamine;

N-(2-Bromo-4-(1-methylethyl)phenyl)-N-ethyl-4-(2-(trifluoromethyl)phenyl)-6-methyl-1,3,5-triazine-2-amine;

N-(4-dimethylamino-2-(trifluoromethyl)phenyl)-N-ethyl-4-(2-(trifluoromethyl)phenyl)-6-methyl-1,3,5-triazine-2-amine;

9-(2-Bromo-4,-isopropylphenyl)-2-methyl-6-(2-trifluoromethyl)phenyl)-8-azapurine and

N-(2-Bromo-4-(1-methylethyl)phenyl)-N-ethyl-4-(2-methylphenyl)-6-methyl-2-pyrimidineamine; and

N-(2-Bromo-4-)-(1-methylethyl)phenyl)-N-ethyl-4-(2,6-dichlorophenyl)-6-methyl-2-pyrimidineamine.

6. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of claim 2.

7. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of claim 3.

8. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of claim 4.

9. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of claim 5.

10. A method of treating affective disorder, anxiety, depression, headache, irritable bowel syndrome, post-traumatic stress disorder, supranuclear palsy, immune suppression, Alzheimer's disease, gastrointestinal diseases, anorexia nervosa or other feeding disorder, drug addiction, drug or alcohol withdrawal symptoms, inflammatory diseases, cardiovascular or heart-related diseases, fertility problems, human immunodeficiency virus infections, hemorrhagic stress, obesity, infertility, head and spinal cord traumas, epilepsy, stroke, ulcers, amyotrophic lateral sclerosis, hypoglycemia or a disorder the treatment of which can be effected or facilitated by antagonizing CRF, including but not limited to disorders induced or facilitated by CRF, in mammals, comprising: administering to the mammal a

therapeutically effective amount of a compound of formula claim 2.

11. A method of treating affective disorder, anxiety, depression, headache, irritable bowel syndrome, post-traumatic stress disorder, supranuclear palsy, immune suppression, Alzheimer's disease, gastrointestinal diseases, anorexia nervosa or other feeding disorder, drug addiction, drug or alcohol withdrawal symptoms, inflammatory diseases, cardiovascular or heart-related diseases, fertility problems, human immunodeficiency virus infections, hemorrhagic stress, obesity, infertility, head and spinal cord traumas, epilepsy, stroke, ulcers, amyotrophic lateral sclerosis, hypoglycemia or a disorder the treatment of which can be effected or facilitated by antagonizing CRF, including but not limited to disorders induced or facilitated by CRF, in mammals, comprising: administering to the mammal a therapeutically effective amount of a compound claim 3.

12. A method of treating affective disorder, anxiety, depression, headache, irritable bowel syndrome, post-traumatic stress disorder, supranuclear palsy, immune suppression, Alzheimer's disease, gastrointestinal diseases, anorexia nervosa or other feeding disorder, drug addiction, drug or alcohol withdrawal symptoms, inflammatory diseases, cardiovascular or heart-related diseases, fertility problems, human immunodeficiency virus infections, hemorrhagic stress, obesity, infertility, head and spinal cord traumas, epilepsy, stroke, ulcers, amyotrophic lateral sclerosis, hypoglycemia or a disorder the treatment of which can be effected or facilitated by antagonizing CRF, including but not limited to disorders induced or facilitated by CRF, in

mammals, comprising: administering to the mammal a therapeutically effective amount of a compound of formula claim 4.

13. A method of treating affective disorder, anxiety, depression, headache, irritable bowel syndrome, post-traumatic stress disorder, supranuclear palsy, immune suppression, Alzheimer's disease, gastrointestinal diseases, anorexia nervosa or other feeding disorder, drug addiction, drug or alcohol withdrawal symptoms, inflammatory diseases, cardiovascular or heart-related diseases, fertility problems, human immunodeficiency virus infections, hemorrhagic stress, obesity, infertility, head and spinal cord traumas, epilepsy, stroke, ulcers, amyotrophic lateral sclerosis, hypoglycemia or a disorder the treatment of which can be effected or facilitated by antagonizing CRF, including but not limited to disorders induced or facilitated by CRF, in mammals, comprising: administering to the mammal a therapeutically effective amount of a compound claim 5.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 98/13840

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D239/42 C07D251/22 C07D473/40 C07D401/04 C07D487/04
A61K31/505 //(C07D487/04,249:00,239:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 10506 A (DU PONT) 20 April 1995 cited in the application see claims; tables 1-16	1-4,6-13
A	WO 95 09847 A (CIBA-GEIGY) 13 April 1995 see the whole document	2,6-9

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 October 1998	30/10/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Francois, J

3

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inter. ...nal Application No
PCT/US 98/13840

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	CHEMICAL ABSTRACTS, vol. 108, no. 15, 1988 Columbus, Ohio, US; abstract no. 131665s, KRISHNA JOSHI ET AL.: "SYNTHESIS OF SOME NEW FLUORINE CONTAINING 1H-PYRAZOLO(3,4-B)PYRIDINES" page 742; column 2; XP002081111 see abstract & J.INDIAN CHEM. SOC., vol. 64, no. 6, 1987, pages 372-373, INDIA ---	1,2,6-13
A	CHEMICAL ABSTRACTS, vol. 90, no. 17, 1979 Columbus, Ohio, US; abstract no. 137763d, S.ROBEV: "SYNTHESIS OF 2,6,9-TRISUBSTITUTED 7H-PURIN-8-ONES." page 510; column 2; XP002081112 see abstract & DOKL.BOLG.AKAD.NAUK, vol. 31, no. 9, 1978, pages 1131-1134, BULG. ---	2,6-9
P,A	WO 97 35539 A (DU PONT) 2 October 1997 see page 126 - page 150 -----	1

3

INTERNATIONAL SEARCH REPORT

In. ..ational application No.

PCT/US 98/ 13840

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 10-13
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 10-13 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

. .ormation on patent family members

Interr nal Application No
PCT/US 98/13840

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9510506 A	20-04-1995	AU 692484 B	11-06-1998
		AU 8012294 A	04-05-1995
		BR 9407799 A	06-05-1997
		CA 2174080 A	20-04-1995
		CN 1142817 A	12-02-1997
		CZ 9601014 A	13-11-1996
		EP 0723533 A	31-07-1996
		FI 961599 A	07-06-1996
		HR 940664 A	31-12-1996
		HU 74464 A	30-12-1996
		JP 9504520 T	06-05-1997
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		ZA 9407921 A	11-04-1996
WO 9509847 A	13-04-1995	AU 693475 B	02-07-1998
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		CA 2148931 A	13-04-1995
		EP 0672035 A	20-09-1995
		JP 8503971 T	30-04-1996
		US 5612340 A	18-03-1997
WO 9735539 A	02-10-1997	AU 2545897 A	17-10-1997

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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A61K 31/165, C07C 235/56

A1

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(30) Priority Data:

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9810355.9	15 May 1998 (15.05.98)	GB

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(74) Agent: TAIT, Brian, Steele; Zeneca Pharmaceuticals, Intellectual Property Dept., Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG (GB).

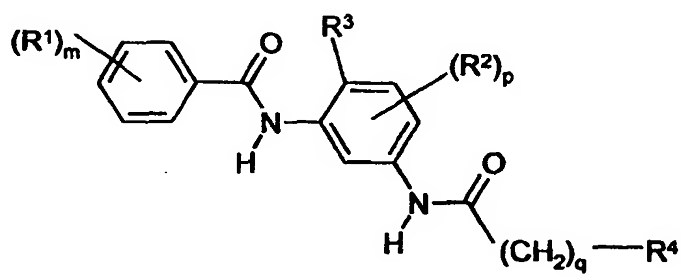
(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: AMIDE DERIVATIVES FOR THE TREATMENT OF DISEASES MEDIATED BY CYTOKINES

(57) Abstract

The invention concerns the use of amide derivatives of formula (I) wherein: R^1 and R^2 are substituents such as hydroxy, C_{1-6}alkoxy, mercapto, C_{1-6}alkylthio, amino, C_{1-6}alkylamino and di-(C_{1-6}alkyl)amino; m and p are independently 0–3; R^3 is C_{1-4}alkyl; q is 0–4; and R^4 is aryl or cycloalkyl; or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in the treatment of diseases or medical conditions mediated by cytokines.



(I)

AMIDE DERIVATIVES FOR THE TREATMENT OF DISEASES MEDIATED BY CYTOKINES

This invention concerns the use of certain amide derivatives as inhibitors of cytokine mediated disease. The invention also concerns certain novel amide derivatives, processes for the manufacture of said novel amide derivatives, pharmaceutical compositions containing them and their use in therapeutic methods, for example by virtue of inhibition of cytokine mediated disease.

The amide derivatives disclosed in the present invention are inhibitors of the production of cytokines such as Tumour Necrosis Factor (hereinafter TNF), for example TNFα, and various members of the interleukin (hereinafter IL) family, for example IL-1, IL-6 and IL-8. Accordingly the compounds of the invention will be useful in the treatment of diseases or medical conditions in which excessive production of cytokines occurs, for example excessive production of TNFα or IL-1. It is known that cytokines are produced by a wide variety of cells such as monocytes and macrophages and that they give rise to a variety of physiological effects which are believed to be important in disease or medical conditions such as inflammation and immunoregulation. For example, TNFα and IL-1 have been implicated in the cell signalling cascade which is believed to contribute to the pathology of disease states such as inflammatory and allergic diseases and cytokine-induced toxicity. It is also known that, in certain cellular systems, TNFα production precedes and mediates the production of other cytokines such as IL-1.

Abnormal levels of cytokines have also been implicated in, for example, the production of physiologically-active eicosanoids such as the prostaglandins and leukotrienes, the stimulation of the release of proteolytic enzymes such as collagenase, the activation of the immune system, for example by stimulation of T-helper cells, the activation of osteoclast activity leading to the resorption of calcium, the stimulation of the release of proteoglycans from, for example, cartilage, the stimulation of cell proliferation and to angiogenesis.

Cytokines are also believed to be implicated in the production and development of disease states such as inflammatory and allergic diseases, for example inflammation of the joints (especially rheumatoid arthritis, osteoarthritis and gout), inflammation of the gastrointestinal tract (especially inflammatory bowel disease, ulcerative colitis, Crohn's disease and gastritis), skin disease (especially psoriasis, eczema and dermatitis) and

respiratory disease (especially asthma, bronchitis, allergic rhinitis and adult respiratory distress syndrome), and in the production and development of various cardiovascular and cerebrovascular disorders such as myocardial infarction, the formation of atherosclerotic plaques, hypertension, platelet aggregation, angina, stroke, reperfusion injury, vascular injury including restenosis and peripheral vascular disease, and, for example, various disorders of bone metabolism such as osteoporosis (including senile and postmenopausal osteoporosis), Paget's disease, bone metastases, hypercalcaemia, hyperparathyroidism, osteosclerosis, osteoperosis and periodontitis, and the abnormal changes in bone metabolism which may accompany rheumatoid arthritis and osteoarthritis. Excessive cytokine production has also been implicated in mediating certain complications of bacterial, fungal and/or viral infections such as endotoxic shock, septic shock and toxic shock syndrome and in mediating certain complications of CNS surgery or injury such as neurotrauma and ischaemic stroke. Excessive cytokine production has also been implicated in mediating or exacerbating the development of diseases involving cartilage or muscle resorption, pulmonary fibrosis, cirrhosis, renal fibrosis, the cachexia found in certain chronic diseases such as malignant disease and acquired immune deficiency syndrome (AIDS), tumour invasiveness and tumour metastasis and multiple sclerosis.

Evidence of the central role played by TNFα in the cell signalling cascade which gives rise to rheumatoid arthritis is provided by the efficacy in clinical studies of antibodies of TNFα (The Lancet, 1994, 344, 1125 and British Journal of Rheumatology, 1995, 34, 334).

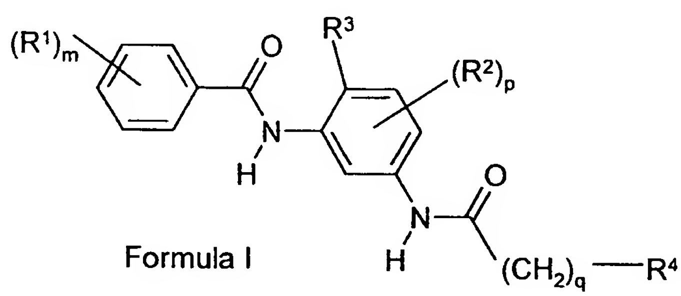
Thus cytokines such as TNFα and IL-1 are believed to be important mediators of a considerable range of diseases and medical conditions. Accordingly it is expected that inhibition of the production of and/or effects of these cytokines will be of benefit in the prophylaxis, control or treatment of such diseases and medical conditions.

Without wishing to imply that the compounds disclosed in the present invention possess pharmacological activity only by virtue of an effect on a single biological process, it is believed that the compounds inhibit the effects of cytokines by virtue of inhibition of the enzyme p38 kinase. P38 kinase, otherwise known as cytokine suppressive binding protein (hereinafter CSBP) and reactivating kinase (hereinafter RK), is a member of the mitogen-activated protein (hereinafter MAP) kinase family of enzymes which is known to be activated by physiological stress such as that induced by ionising radiation, cytotoxic agents, and

toxins, for example endotoxins such as bacterial lipopolysaccharide, and by a variety of agents such as the cytokines, for example TNFα and IL-1. It is known that p38 kinase phosphorylates certain intracellular proteins which are involved in the cascade of enzymatic steps which leads to the biosynthesis and excretion of cytokines such as TNFα and IL-1. Known inhibitors of p38 kinase have been reviewed by G J Hanson in Expert Opinions on Therapeutic Patents, 1997, 7, 729-733. p38 kinase is known to exist in isoforms identified as p38α and p38β.

The compounds disclosed in the present invention are inhibitors of the production of cytokines such as TNF, in particular of TNFα, and various interleukins, in particular IL-1.

According to one aspect of the present invention there is provided the use of a compound of the Formula I



Formula I

wherein:

R^1 and R^2, which may be the same or different are selected from hydroxy, C_{1-6}alkoxy, mercapto, C_{1-6}alkylthio, amino, C_{1-6}alkylamino, di-(C_{1-6}alkyl)amino, carboxy, C_{1-6}alkoxycarbonyl, carbamoyl, C_{1-6}alkylcarbamoyl, di-C_{1-6}alkylcarbamoyl, C_{1-6}alkylsulphonyl, arylsulphonyl, C_{1-6}alkylaminosulphonyl, di-(C_{1-6}alkyl)aminosulphonyl, nitro, cyano, cyanoC_{1-6}alkyl, hydroxyC_{1-6}alkyl, aminoC_{1-6}alkyl, C_{1-6}alkanoylamino, C_{1-6}alkoxycarbonylamino, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, C_{1-6}alkyl, halo, trifluoromethyl, aryl, arylC_{1-6}alkyl, arylC_{1-6}alkoxy, heteroaryl, heteroarylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl;

m and p, are independently 0-3, and when m and/or p is 2 or 3 each R group may be the same or different;

R^3 is C_{1-4}alkyl;

q is 0-4;

R^4 is aryl or cycloalkyl wherein R^4 is optionally substituted with up to 3 substituents having any value defined for R^1;

or a pharmaceutically-acceptable salt or in vivo cleavable ester thereof in the manufacture of a medicament for use in the treatment of diseases or medical conditions mediated by cytokines.

In a further aspect the present invention provides a method of treating diseases or medical conditions mediated by cytokines which comprises administering to a warm-blooded animal an effective amount of a compound of the Formula I, or a pharmaceutically-acceptable salt or in vivo cleavable ester thereof.

In a further aspect the present invention provides the use of a compound of the Formula I, or a pharmaceutically-acceptable salt or in vivo cleavable ester thereof, in the manufacture of a medicament for use in the treatment of diseases or medical conditions mediated by TNF, IL-1, IL-6 or IL-8.

In a further aspect the present invention provides a method of treating diseases or medical conditions mediated by TNF, IL-1, IL-6 or IL-8 which comprises administering to a warm-blooded animal an effective amount of a compound of the Formula I, or a pharmaceutically-acceptable salt or in vivo cleavable ester thereof.

In a further aspect the present invention provides the use of a compound of the Formula I, or a pharmaceutically-acceptable salt or in vivo cleavable ester thereof, in the manufacture of a medicament for use in the treatment of diseases or medical conditions mediated by TNF.

In a further aspect the present invention provides a method of treating diseases or medical conditions mediated by TNF which comprises administering to a warm-blooded animal an effective amount of a compound of the Formula I, or a pharmaceutically-acceptable salt or in vivo cleavable ester thereof.

In a further aspect the present invention provides the use of a compound of the Formula I, or a pharmaceutically-acceptable salt or in vivo cleavable ester thereof, in the manufacture of a medicament for use in inhibiting TNF, IL-1, IL-6 or IL-8.

In a further aspect the present invention provides a method of inhibiting TNF, IL-1, IL-6 or IL-8 which comprises administering to a warm-blooded animal an effective amount of a compound of the Formula I, or a pharmaceutically-acceptable salt or in vivo cleavable ester thereof.

In a further aspect the present invention provides the use of a compound of the Formula I, or a pharmaceutically-acceptable salt or in vivo cleavable ester thereof, in the

manufacture of a medicament for use in inhibiting TNF.

In a further aspect the present invention provides a method of inhibiting TNF which comprises administering to a warm-blooded animal an effective amount of a compound of the Formula I, or a pharmaceutically-acceptable salt or in vivo cleavable ester thereof.

In a further aspect the present invention provides the use of a compound of the Formula I, or a pharmaceutically-acceptable salt or in vivo cleavable ester thereof, in the manufacture of a medicament for use in the treatment of diseases or medical conditions mediated by p38 kinase.

In a further aspect the present invention provides a method of treating diseases or medical conditions mediated by p38 kinase which comprises administering to a warm-blooded animal an effective amount of a compound of the Formula I, or a pharmaceutically-acceptable salt or in vivo cleavable ester thereof.

In a further aspect the present invention provides the use of a compound of the Formula I, or a pharmaceutically-acceptable salt or in vivo cleavable ester thereof, in the manufacture of a medicament for use in the production of a p38 kinase inhibitory effect.

In a further aspect the present invention provides a method of providing a p38 kinase inhibitory effect which comprises administering to a warm-blooded animal an effective amount of a compound of the Formula I, or a pharmaceutically-acceptable salt or in vivo cleavable ester thereof.

In a further aspect the present invention provides the use of a compound of the Formula I, or a pharmaceutically-acceptable salt or in vivo cleavable ester thereof, in the manufacture of a medicament for use in the treatment of rheumatoid arthritis, asthma, irritable bowel disease, multiple sclerosis, AIDS, septic shock, ischaemic heart disease or psoriasis.

In a further aspect the present invention provides a method of treating rheumatoid arthritis, asthma, irritable bowel disease, multiple sclerosis, AIDS, septic shock, ischaemic heart disease or psoriasis which comprises administering to a warm-blooded animal an effective amount of a compound of the Formula I, or a pharmaceutically-acceptable salt or in vivo cleavable ester thereof.

Certain compounds falling within the scope of Formula (I) are known to upregulate LDL receptors (Brown et al. in Atherosclerosis (1994) 109:113-114, Halley et al. in J. Med. Chem., (1996) 39: 3343-3356). The compounds listed immediately hereinafter were disclosed

in that J. Med. Chem. paper and fall within the scope of the compound definition disclosed hereinbefore :-

N-[5-(3-cyclohexylpropionamido)-2-methylphenyl]-4-hydroxybenzamide,
N-[5-(3-cyclohexylpropionamido)-2-methylphenyl]-4-acetoxybenzamide,
N-[5-(3-cyclohexylpropionamido)-2-methylphenyl]benzamide,
N-[5-(3-cyclohexylpropionamido)-2-methylphenyl]-3-hydroxybenzamide,
N-[5-(3-cyclohexylpropionamido)-2-methylphenyl]-2-hydroxybenzamide,
N-[5-(3-cyclohexylpropionamido)-2-methylphenyl]-4-methoxycarbonylbenzamide,
N-[5-(3-cyclohexylpropionamido)-2-methylphenyl]-4-hydroxymethylbenzamide,
N-[5-(3-cyclohexylpropionamido)-2-methylphenyl]-4-nitrobenzamide,
N-[5-(3-cyclohexylpropionamido)-2-methylphenyl]-4-aminobenzamide,
N-[5-(2-cyclohexylacetamido)-2-methylphenyl]-4-acetoxybenzamide,
N-[5-(4-cyclohexylbutyrylamino)-2-methylphenyl]-4-hydroxybenzamide,
N-[5-(3-cyclopentylpropionamido)-2-methylphenyl]-4-hydroxybenzamide,
N-[5-(3-phenylpropionamido)-2-methylphenyl]-4-hydroxybenzamide,
N-[5-(4-cyclohexylbutyrylamino)-2-methylphenyl]-4-acetoxybenzamide,
N-[5-(3-phenylpropionamido)-2-methylphenyl]-4-acetoxybenzamide and
N-[5-(3-cyclopentylpropionamido)-2-methylphenyl]-4-acetoxybenzamide.

From these compounds the following representative examples have now been found to possess p38 kinase inhibitory activity:-

N-[5-(3-cyclopentylpropionamido)-2-methylphenyl]-4-hydroxybenzamide,
N-[5-(3-cyclohexylpropionamido)-2-methylphenyl]-3-hydroxybenzamide,
N-[5-(3-cyclohexylpropionamido)-2-methylphenyl]-4-hydroxybenzamide,
N-[5-(3-cyclohexylpropionamido)-2-methylphenyl]-4-aminobenzamide and
N-[5-(4-cyclohexylbutyrylamino)-2-methylphenyl]-4-hydroxybenzamide.

Copending International Patent Application PCT/GB97/03102 which gave rise on 28May1998 to International Application Publication No. WO 98/22103 concerns certain bisamide derivatives which are stated to possess inhibitory activity against the enzyme raf kinase and thereby to be useful in the treatment of diseases such as cancer. The compounds disclosed therein as examples are listed immediately hereinafter and fall within the scope of the compound definition disclosed hereinbefore :-

N-[5-(2-bicyclo[2.2.1]hept-2-ylacetamido)-2-methylphenyl]-4-hydroxybenzamide, N-{5-[2-(3,4-dichlorophenyl)acetamido]-2-methylphenyl}-4-hydroxybenzamide and N-[5-(3-dimethylaminobenzamido)-2-methylphenyl]-4-hydroxybenzamide. These compounds have now been found to possess p38 kinase inhibitory activity.

In a further aspect the present invention provides a compound of the Formula I as defined hereinbefore for use in a method of treatment of the human or animal body by therapy, in particular for use in the treatment of diseases or medical conditions mediated by cytokines and, more particularly, for use in inhibiting TNF, except that
N-[5-(3-cyclohexylpropionamido)-2-methylphenyl]-4-hydroxybenzamide,
N-[5-(3-cyclohexylpropionamido)-2-methylphenyl]-4-acetoxybenzamide,
N-[5-(3-cyclohexylpropionamido)-2-methylphenyl]benzamide,
N-[5-(3-cyclohexylpropionamido)-2-methylphenyl]-3-hydroxybenzamide,
N-[5-(3-cyclohexylpropionamido)-2-methylphenyl]-2-hydroxybenzamide,
N-[5-(3-cyclohexylpropionamido)-2-methylphenyl]-4-methoxycarbonylbenzamide,
N-[5-(3-cyclohexylpropionamido)-2-methylphenyl]-4-hydroxymethylbenzamide,
N-[5-(3-cyclohexylpropionamido)-2-methylphenyl]-4-nitrobenzamide,
N-[5-(3-cyclohexylpropionamido)-2-methylphenyl]-4-aminobenzamide,
N-[5-(2-cyclohexylacetamido)-2-methylphenyl]-4-acetoxybenzamide,
N-[5-(4-cyclohexylbutyrylamino)-2-methylphenyl]-4-hydroxybenzamide,
N-[5-(3-cyclopentylpropionamido)-2-methylphenyl]-4-hydroxybenzamide,
N-[5-(3-phenylpropionamido)-2-methylphenyl]-4-hydroxybenzamide,
N-[5-(2-bicyclo[2.2.1]hept-2-ylacetamido)-2-methylphenyl]-4-hydroxybenzamide,
N-{5-[2-(3,4-dichlorophenyl)acetamido]-2-methylphenyl}-4-hydroxybenzamide,
N-[5-(3-dimethylaminobenzamido)-2-methylphenyl]-4-hydroxybenzamide,
N-[5-(4-cyclohexylbutyrylamino)-2-methylphenyl]-4-acetoxybenzamide,
N-[5-(3-phenylpropionamido)-2-methylphenyl]-4-acetoxybenzamide and
N-[5-(3-cyclopentylpropionamido)-2-methylphenyl]-4-acetoxybenzamide
are excluded.

Certain other compounds within the scope of Formula I are known outside the pharmaceutical field :-

(a) Japanese Patent Application No. 04065513 (Chemical Abstracts, 117, 50742)

discloses the compound N-[5-(4-carbamoylbenzamido)-2-methylphenyl]-4-carbamoylbenzamide as a chemical intermediate;

(b) Japanese Patent Application No. 62198852 (Chemical Abstracts, 109, 14765) discloses the compound N-[5-(3,4,5-trihydroxybenzamido)-2-methylphenyl]-3,4,5-trihydroxybenzamide as a chemical intermediate;

(c) US Patent No. 4,410,681 (Chemical Abstracts, 100, 52612) and US Patent No. 4,367,328 (Chemical Abstracts, 98, 144515) each disclose the compound N-[5-(2-hydroxybenzamido)-2-methylphenyl]-2-hydroxybenzamide as a chemical intermediate;

(d) Japanese Patent Application No. 53079835 (Chemical Abstracts, 89, 147671) discloses the compound N-{5-[4-carboxy-3-(2-dimethylaminoethoxycarbonyl)benzamido]-2-methylphenyl}-4-carboxy-3-(2-dimethylaminoethoxycarbonyl)benzamide as a chemical intermediate;

(e) German Patent Application No. DE 2552609 (Chemical Abstracts, 85, 192408) discloses the compounds N-[5-(3-methoxycarbonylbenzamido)-2-methylphenyl]-3-methoxycarbonylbenzamide and N-[5-(4-methoxycarbonylbenzamido)-2-methylphenyl]-4-methoxycarbonylbenzamide as chemical intermediates;

(f) Japanese Patent Application No. 50105558 (Chemical Abstracts, 84, 45269) discloses the compound N-[5-(4-methoxybenzamido)-2-methylphenyl]-4-methoxybenzamide as a chemical intermediate;

(g) Japanese Patent Application No. 61204221 (Chemical Abstracts, 106, 34087) discloses the compound N-(5-benzamido-2-methylphenyl)benzamide as a chemical intermediate;

(h) Netherlands Patent Application No. 6514411 (Chemical Abstracts, 65, 10706f) discloses certain indolizine derivatives as aromatic pigments;

(i) Chemical Abstracts, 64, 19459g concerns reduction of some alkyl-substituted dinitrobenzenes and discloses the compound N-(5-benzamido-2-ethylphenyl)benzamide; and

(j) Chemical Abstracts, 62, 3959d discloses the compound N-[5-(4-nitrobenzamido)-2-ethylphenyl]-4-nitrobenzamide.

The reader is directed to these references for general guidance on synthesis of compounds within the scope of Formula I.

In this specification the generic term "alkyl" includes both straight-chain and branched-chain alkyl groups. However references to individual alkyl groups such as "propyl" are specific for the straight-chain version only and references to individual branched-chain alkyl groups such as "isopropyl" are specific for the branched-chain version only. An analogous convention applies to other generic terms.

"Aryl" in terms such as "aryl", "arylC_{1-6}alkyl", "arylsulphonyl" and "arylC_{1-6}alkoxy" typically means phenyl or naphthyl, preferably phenyl. An "arylC_{1-6}alkyl" group means, for example, arylmethyl or 2-arylethyl. An "arylC_{1-6}alkoxy" group means, for example, arylmethoxy or 2-arylethoxy. "Heteroaryl" in the terms "heteroaryl" and "heteroarylC_{1-6}alkyl" means an aromatic mono- or bicyclic 5-10 membered ring with up to five ring heteroatoms selected from nitrogen, oxygen and sulphur. Examples of 'heteroaryl' include thienyl, pyrrolyl, furyl, imidazolyl, oxazolyl, thiazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyrazinyl, pyridazinyl, pyrimidinyl, pyridyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, indazolyl, quinolyl, isoquinolyl, quinazolinyl, quinoxalinyl and cinnolinyl. A "heteroarylC_{1-6}alkyl" group means, for example, heteroarylmethyl or 2-heteroarylethyl. "Heterocyclyl" in the terms "heterocyclyl" and "heterocyclylC_{1-6}alkyl" means a non-aromatic mono- or bicyclic 5-10 membered ring with up to five ring hetero atoms selected from nitrogen, oxygen and sulphur. Examples of 'heterocyclyl' include pyrrolinyl, pyrrolidinyl, morpholinyl, piperidinyl, piperazinyl, homopiperidinyl, homopiperazinyl, dihydropyridinyl, tetrahydropyridinyl, dihydropyrimidinyl and tetrahydropyrimidinyl. A "heterocyclylC_{1-6}alkyl" group means, for example, heterocyclylmethyl or 2-heterocyclylethyl. "Cycloalkyl" means a non-aromatic mono- or bicyclic 5-10 membered carbon ring. Examples of "cycloalkyl" include cyclopentyl, cyclohexyl, cycloheptyl, bicyclo[2.2.1]heptyl and bicyclo[4.4.0]decyl.

Typical values for other generic groups include: for C_{1-6}alkoxy, for example, methoxy and ethoxy, for C_{1-6}alkylthio, for example, methylthio, for C_{1-6}alkylamino, for example, methylamino, for di-(C_{1-6}alkyl)amino, for example, dimethylamino, for C_{1-6}alkoxycarbonyl, for example, methoxycarbonyl and ethoxycarbonyl, for C_{1-6}alkylcarbamoyl, for example, methylcarbamoyl, for di-C_{1-6}alkylcarbamoyl, for example, dimethylcarbamoyl, for C_{1-6}alkylsulphonyl, for example, methylsulphonyl, for arylsulphonyl, for example,

phenylsulphonyl, for C_{1-6}alkylaminosulphonyl, for example, methylaminosulphonyl, for di-(C_{1-6}alkyl)aminosulphonyl, for example, dimethylaminosulphonyl, for cyanoC_{1-6}alkyl, for example, cyanomethyl, for hydroxyC_{1-6}alkyl, for example, hydroxymethyl, for aminoC_{1-6}alkyl, for example, aminomethyl, for C_{1-6}alkanoylamino, for example, formamido and acetamido, for C_{1-6}alkoxycarbonylamino, for example, methoxycarbonylamino, for C_{1-6}alkanoyl, for example, formyl and acetyl, for C_{1-6}alkanoyloxy, for example, acetoxy, for C_{1-6}alkyl or C_{1-4}alkyl, for example, methyl, ethyl, propyl, isopropyl and tert-butyl, for halo, for example, fluoro, chloro and bromo, for aryl, for example, phenyl, for arylC_{1-6}alkyl, for example, benzyl, and for arylC_{1-6}alkoxy, for example, benzyloxy.

Any ring in R^1 or R^2 or any ring in a substituent on R^4 may be optionally substituted, for example by up to 3 substituents. Suitable substituents include hydroxy, C_{1-6}alkoxy, mercapto, C_{1-6}alkylthio, amino, C_{1-6}alkylamino, di-(C_{1-6}alkyl)amino, carboxy, carbamoyl, C_{1-6}alkylcarbamoyl, di-C_{1-6}alkylcarbamoyl, C_{1-6}alkylsulphonyl, arylsulphonyl, C_{1-6}alkylaminosulphonyl, di-(C_{1-6}alkyl)aminosulphonyl, nitro, cyano, cyanoC_{1-6}alkyl, hydroxyC_{1-6}alkyl, aminoC_{1-6}alkyl, C_{1-6}alkanoylamino, C_{1-6}alkoxycarbonylamino, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, C_{1-6}alkyl, halo and trifluoromethyl. For example, when R^1 or a substituent on R^4 is a heterocyclyl or heterocyclylC_{1-6}alkyl group the heterocyclyl ring may bear up to 3 substituents selected from hydroxy, C_{1-6}alkoxy, carboxy, carbamoyl, C_{1-6}alkylcarbamoyl, di-C_{1-6}alkylcarbamoyl, C_{1-6}alkanoyl, C_{1-6}alkyl, halo and trifluoromethyl. Examples of such substituted heterocyclyl rings include 4-carbamoylpiperidin-1-yl, 4-methylpiperazin-1-yl and 4-acetylpiperazin-1-yl.

It is to be understood that, insofar as certain of the compounds of Formula I defined above may exist in optically active or racemic forms by virtue of one or more asymmetric carbon atoms, the invention includes in its definition any such optically active or racemic form which possesses the property of inhibiting cytokines, in particular TNF. The synthesis of optically active forms may be carried out by standard techniques of organic chemistry well known in the art, for example by synthesis from optically active starting materials or by resolution of a racemic form. Similarly, inhibitory properties against TNF may be evaluated using the standard laboratory techniques referred to hereinafter.

Preferably R^1 is hydroxy, C_{1-6}alkoxy, C_{1-6}alkoxycarbonyl, carbamoyl, C_{1-6}alkylcarbamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, C_{1-6}alkyl, halo,

trifluoromethyl, phenyl or phenyl C_{1-6}alkoxy.

Most preferably R^1 is hydroxy, C_{1-6}alkoxy, C_{1-6}alkanoylamino or C_{1-6}alkanoyl.

Preferably m is 1 or 2.

Preferably R^3 is methyl.

Preferably R^2 is carboxy, C_{1-6}alkoxycarbonyl, carbamoyl, C_{1-6}alkylcarbamoyl or di-(C_{1-6}alkyl)carbamoyl.

Preferably p is 0.

Preferably R^4 is phenyl, cyclohexyl or cyclopentyl.

More preferably R^4 is phenyl or cyclohexyl.

Preferred substituents for aryl and cyclohexyl groups in R^4 are hydroxy, C_{1-6}alkoxy, C_{1-6}alkoxycarbonyl, carbamoyl, C_{1-6}alkylcarbamoyl, C_{1-6}alkanoylamino, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, C_{1-6}alkyl, halo, trifluoromethyl, phenyl, phenylC_{1-6}alkoxy, nitro, cyano, amino, C_{1-6}alkylamino or di-(C_{1-6}alkyl)amino.

More preferably substituents for aryl and cyclohexyl in R^4 are selected from cyano, dimethylamino, methoxy, ethoxy, fluoro, chloro, nitro and phenyl.

In a further aspect the present invention provides novel compounds within the scope of the compounds of the Formula I as defined hereinbefore.

A particular group of compounds of the invention includes, for example, amide derivatives of the Formula I, or pharmaceutically-acceptable salts thereof, wherein:-

(a) q is 1, 2, 3 or 4 and R^4 is cycloalkyl; and R^1, R^2, R^3, m and p have any of the meanings defined hereinbefore; and

(b) q is 0 and R^4 is phenyl which is optionally substituted with up to 3 substituents having any value defined hereinbefore for R^1; and R^1, R^2, R^3, m and p have any of the meanings defined hereinbefore.

A particular novel compound of the invention is an amide derivative of the Formula I wherein R^1 is hydroxy, methoxy, ethoxy, propoxy, isopropoxy, butoxy, amino, methylamino, dimethylamino, carboxy, methoxycarbonyl, nitro, cyano, acetamido, acetyl, acetoxy, methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, fluoro, chloro, bromo, trifluoromethyl, pyrrolidin-1-yl, piperidino, morpholino, 4-thiamorpholino, piperazin-1-yl, 4-methylpiperazin-1-yl, 4-methylhomopiperazin-1-yl, pyrrolidin-1-ylmethyl, piperidinomethyl, 4-carbamoylpiperidin-1-ylmethyl, morpholinomethyl,

4-thiamorpholinomethyl, piperazin-1-ylmethyl, 4-methylpiperazin-1-ylmethyl, 4-ethylpiperazin-1-ylmethyl, 4-propylpiperazin-1-ylmethyl, 4-isopropylpiperazin-1-ylmethyl, 4-acetylpiperazin-1-ylmethyl and 4-methylhomopiperazin-1-ylmethyl;

m is 1, 2 or 3;

p is 0;

R^3 is methyl;

q is 0; and

R^4 is phenyl which is optionally substituted with 1 or 2 substituents selected from hydroxy, methoxy, ethoxy, amino, methylamino, dimethylamino, methoxycarbonyl, nitro, cyano, acetamido, fluoro, chloro, bromo, trifluoromethyl, phenyl, benzyloxy, pyrrolidin-1-yl, piperidino, morpholino, 4-thiamorpholino, piperazin-1-yl, 4-methylpiperazin-1-yl, 4-methylhomopiperazin-1-yl, pyrrolidin-1-ylmethyl, piperidinomethyl, 4-carbamoylpiperidin-1-ylmethyl, morpholinomethyl, 4-thiamorpholinomethyl, piperazin-1-ylmethyl, 4-methylpiperazin-1-ylmethyl, 4-ethylpiperazin-1-ylmethyl, 4-propylpiperazin-1-ylmethyl, 4-isopropylpiperazin-1-ylmethyl, 4-acetylpiperazin-1-ylmethyl and 4-methylhomopiperazin-1-ylmethyl;

or a pharmaceutically-acceptable salt thereof;

except that N-[5-(3-dimethylaminobenzamido)-2-methylphenyl]-4-hydroxybenzamide, N-[5-(2-hydroxybenzamido)-2-methylphenyl]-2-hydroxybenzamide, N-[5-(4-methoxybenzamido)-2-methylphenyl]-4-methoxybenzamide, N-[5-(3-methoxycarbonylbenzamido)-2-methylphenyl]-3-methoxycarbonylbenzamide and N-[5-(4-methoxycarbonylbenzamido)-2-methylphenyl]-4-methoxycarbonylbenzamide are excluded.

A preferred novel compound of the invention is an amide derivative of the Formula I wherein R^1 is hydroxy, methoxy, ethoxy, isopropoxy, carboxy, methoxycarbonyl, nitro, cyano, acetyl, acetoxy, methyl, ethyl, propyl, fluoro, chloro or trifluoromethyl;

m is 1, 2 or 3;

p is 0;

R^3 is methyl;

q is 0; and

R^4 is phenyl which is optionally substituted with 1 or 2 substituents selected from hydroxy, methoxy, amino, methylamino, dimethylamino, nitro, cyano, fluoro, chloro, bromo, trifluoromethyl and benzyloxy;
or a pharmaceutically-acceptable salt thereof;
except that N-[5-(3-dimethylaminobenzamido)-2-methylphenyl]-4-hydroxybenzamide, N-[5-(2-hydroxybenzamido)-2-methylphenyl]-2-hydroxybenzamide and N-[5-(4-methoxybenzamido)-2-methylphenyl]-4-methoxybenzamide are excluded.

A more preferred novel compound of the invention is an amide derivative of the Formula I
wherein R^1 is hydroxy, methoxy, carboxy or acetoxy;
m is 1 or 2;
p is 0;
R^3 is methyl;
q is 0; and
R^4 is phenyl which is optionally substituted with a substituent selected from hydroxy, dimethylamino, cyano and benzyloxy;
or a pharmaceutically-acceptable salt thereof;
except that N-[5-(3-dimethylaminobenzamido)-2-methylphenyl]-4-hydroxybenzamide and N-[5-(2-hydroxybenzamido)-2-methylphenyl]-2-hydroxybenzamide are excluded.

A further preferred novel compound of the invention is an amide derivative of the Formula I
wherein R^1 is hydroxy, methoxy, ethoxy, propoxy, isopropoxy, butoxy, amino, methylamino, dimethylamino, carboxy, methoxycarbonyl, nitro, cyano, acetamido, acetyl, acetoxy, methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, fluoro, chloro, bromo, trifluoromethyl, pyrrolidin-1-yl, piperidino, morpholino, 4-thiamorpholino, piperazin-1-yl, 4-methylpiperazin-1-yl, 4-methylhomopiperazin-1-yl, pyrrolidin-1-ylmethyl, piperidinomethyl, 4-carbamoylpiperidin-1-ylmethyl, morpholinomethyl, 4-thiamorpholinomethyl, piperazin-1-ylmethyl, 4-methylpiperazin-1-ylmethyl, 4-ethylpiperazin-1-ylmethyl, 4-propylpiperazin-1-ylmethyl, 4-isopropylpiperazin-1-ylmethyl, 4-acetylpiperazin-1-ylmethyl and 4-methylhomopiperazin-1-ylmethyl;

m is 1, 2 or 3;

p is 0;

R^3 is methyl;

q is 1, 2, 3 or 4; and

R^4 is cyclopentyl or cyclohexyl;

or a pharmaceutically-acceptable salt thereof;

except that N-[5-(3-cyclohexylpropionamido)-2-methylphenyl]-4-hydroxybenzamide,
N-[5-(3-cyclohexylpropionamido)-2-methylphenyl]-4-acetoxybenzamide,
N-[5-(3-cyclohexylpropionamido)-2-methylphenyl]-3-hydroxybenzamide,
N-[5-(3-cyclohexylpropionamido)-2-methylphenyl]-2-hydroxybenzamide,
N-[5-(3-cyclohexylpropionamido)-2-methylphenyl]-4-methoxycarbonylbenzamide,
N-[5-(3-cyclohexylpropionamido)-2-methylphenyl]-4-nitrobenzamide,
N-[5-(3-cyclohexylpropionamido)-2-methylphenyl]-4-aminobenzamide,
N-[5-(2-cyclohexylacetamido)-2-methylphenyl]-4-acetoxybenzamide,
N-[5-(4-cyclohexylbutyrylamino)-2-methylphenyl]-4-hydroxybenzamide,
N-[5-(3-cyclopentylpropionamido)-2-methylphenyl]-4-hydroxybenzamide,
N-[5-(4-cyclohexylbutyrylamino)-2-methylphenyl]-4-acetoxybenzamide and
N-[5-(3-cyclopentylpropionamido)-2-methylphenyl]-4-acetoxybenzamide
are excluded.

A further preferred novel compound of the invention is an amide derivative of the Formula I wherein R^1 is hydroxy, methoxy, ethoxy, isopropoxy, carboxy, methoxycarbonyl, nitro, cyano, acetyl, acetoxy, methyl, ethyl, propyl, fluoro, chloro or trifluoromethyl;

m is 1, 2 or 3;

p is 0;

R^3 is methyl;

q is 1, 2, 3 or 4; and

R^4 is cyclohexyl;

or a pharmaceutically-acceptable salt thereof;

except that N-[5-(3-cyclohexylpropionamido)-2-methylphenyl]-4-hydroxybenzamide,
N-[5-(3-cyclohexylpropionamido)-2-methylphenyl]-4-acetoxybenzamide,
N-[5-(3-cyclohexylpropionamido)-2-methylphenyl]-3-hydroxybenzamide,

N-[5-(3-cyclohexylpropionamido)-2-methylphenyl]-2-hydroxybenzamide,
N-[5-(3-cyclohexylpropionamido)-2-methylphenyl]-4-methoxycarbonylbenzamide,
N-[5-(3-cyclohexylpropionamido)-2-methylphenyl]-4-nitrobenzamide,
N-[5-(2-cyclohexylacetamido)-2-methylphenyl]-4-acetoxybenzamide,
N-[5-(4-cyclohexylbutyrylamino)-2-methylphenyl]-4-hydroxybenzamide,
N-[5-(4-cyclohexylbutyrylamino)-2-methylphenyl]-4-acetoxybenzamide and
N-[5-(4-cyclohexylbutyrylamino)-2-methylphenyl]-4-acetoxybenzamide are excluded.

A further more preferred novel compound of the invention is an amide derivative of the Formula I wherein R^1 is hydroxy, methoxy, carboxy or acetoxy;
m is 1 or 2;
p is 0;
R^3 is methyl;
q is 2, 3, or 4; and
R^4 is cyclohexyl;
or a pharmaceutically-acceptable salt thereof;
except that N-[5-(3-cyclohexylpropionamido)-2-methylphenyl]-4-hydroxybenzamide,
N-[5-(3-cyclohexylpropionamido)-2-methylphenyl]-4-acetoxybenzamide,
N-[5-(3-cyclohexylpropionamido)-2-methylphenyl]-3-hydroxybenzamide,
N-[5-(3-cyclohexylpropionamido)-2-methylphenyl]-2-hydroxybenzamide,
N-[5-(4-cyclohexylbutyrylamino)-2-methylphenyl]-4-hydroxybenzamide and
N-[5-(4-cyclohexylbutyrylamino)-2-methylphenyl]-4-acetoxybenzamide are excluded.

Particular compounds for use in the present invention are:
N-[5-(4-cyclohexylbutyrylamino)-2-methylphenyl]-4-hydroxybenzamide;
N-[5-(4-cyanobenzamido)-2-methylphenyl]-4-hydroxybenzamide;
N-[5-(5-cyclohexylvalerylamino)-2-methylphenyl]-4-hydroxybenzamide;
N-[5-(3-cyclohexylpropionamido)-2-methylphenyl]-4-hydroxybenzamide;
N-[5-(3-dimethylaminobenzamido)-2-methylphenyl]-4-hydroxybenzamide;
N-(5-benzamido-2-methylphenyl)-4-hydroxybenzamide;
N-[5-(2-(3,4-dichlorophenyl)acetamido)-2-methylphenyl]-4-hydroxybenzamide;
N-[5-(3,5-dimethoxybenzamido)-2-methylphenyl]-4-hydroxybenzamide;
N-[5-(2-fluoro-6-chlorobenzamido)-2-methylphenyl]-4-hydroxybenzamide;

N-[5-(3-cyclopentylpropionamido)-2-methylphenyl]-4-hydroxybenzamide;
N-[5-(4-phenylbenzamido)-2-methylphenyl]-4-hydroxybenzamide;
N-[5-(2-(4-nitrophenyl)acetamido)-2-methylphenyl]-4-hydroxybenzamide;
N-[5-(2-cyclohexylpropionamido)-2-methylphenyl]-4-acetylbenzamide;
N-[5-(3-dimethylaminobenzamido)-2-methylphenyl]-3,4-dimethoxybenzamide;
N-[5-(3-dimethylaminobenzamido)-2-methylphenyl]-4-methoxybenzamide;
N-[5-(3-cyclohexylpropionamido)-2-methylphenyl]-4-hydroxy-3-methoxybenzamide;
N-[5-(3-cyclohexylpropionamido)-2-methylphenyl]-3,4-dimethoxybenzamide;
N-[5-(3-cyclohexylpropionamido)-2-methylphenyl]-4-methoxybenzamide;
N-[5-(3-cyclohexylpropionamido)-2-methylphenyl]-3-hydroxybenzamide; and
N-[5-(3-cyclohexylpropionamido)-2-methylphenyl]-2-acetamidobenzamide;
and pharmaceutically-acceptable salts thereof.

Particular novel compounds of the present invention are:

N-[5-(3-benzyloxybenzamido)-2-methylphenyl]-3,4-dimethoxybenzamide;
N-[5-(4-cyanobenzamido)-2-methylphenyl]-4-acetoxybenzamide;
N-(5-benzamido-2-methylphenyl)-3,4-dimethoxybenzamide;
N-[5-(4-cyanobenzamido)-2-methylphenyl]-3,4-dimethoxybenzamide;
N-[5-(3-hydroxybenzamido)-2-methylphenyl]-3,4-dimethoxybenzamide;
N-[5-(3-dimethylaminobenzamido)-2-methylphenyl]-4-butoxybenzamide;
N-[5-(3-cyclohexylpropionamido)-2-methylphenyl]-3,4,5-trimethoxybenzamide; and
N-[5-(3-cyclohexylpropionamido)-2-methylphenyl]-4-carboxybenzamide;
and pharmaceutically-acceptable salts thereof.

A further particular novel compound of the present invention is:

N-[2-methyl-5-(3-trifluoromethylbenzamido)phenyl]-3,4-dimethoxybenzamide,
and pharmaceutically-acceptable salts thereof.

In a further aspect of the present invention there is provided a group of novel compounds of the Formula I wherein R^4 is phenyl which bears a basic substituent located at the 3- and/or 4-positions. This group of compounds possesses improved TNFα inhibitory potency in one or both of the PBMC and Human Whole Blood tests described hereinafter.

A particular group of novel compounds according to this aspect of the invention is an amide derivative of the Formula I

wherein R^1 is hydroxy, C_{1-6}alkoxy, carboxy, C_{1-6}alkoxycarbonyl, nitro, cyano, C_{1-6}alkanoylamino, C_{1-6}alkanoyl, C_{1-6}alkyl, halo or trifluoromethyl;

m is 0-3 and when m is 2 or 3 each R^1 group is the same or different;

p is 0;

R^3 is methyl;

q is 0; and

R^4 is phenyl which is substituted with 1 or 2 substituents selected from amino, C_{1-6}alkylamino, di-(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, heteroaryl, heteroarylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl, and when there is 1 substituent it is located at the 3-position and when there are 2 substituents, which may be the same or different, they are located at the 3- and 4-positions;

or a pharmaceutically-acceptable salt thereof;

except that N-[5-(3-dimethylaminobenzamido)-2-methylphenyl]-4-hydroxybenzamide is excluded.

A preferred group of novel compounds according to this aspect of the invention is an amide derivative of the Formula I

wherein R^1 is hydroxy, methoxy, ethoxy, propoxy, isopropoxy, butoxy, carboxy, methoxycarbonyl, nitro, cyano, acetamido, acetyl, methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, fluoro, chloro, bromo or trifluoromethyl;

m is 0-3 and when m is 2 or 3 each R^1 group is the same or different;

p is 0;

R^3 is methyl;

q is 0; and

R^4 is phenyl which is substituted at the 3- or 4-position with a substituent selected from amino, methylamino, dimethylamino, aminomethyl, pyrrolidin-1-yl, piperidino, morpholino, 4-thiamorpholino, piperazin-1-yl, 4-methylpiperazin-1-yl, 4-methylhomopiperazin-1-yl, pyrrolidin-1-ylmethyl, piperidinomethyl, 4-carbamoylpiperidin-1-ylmethyl, morpholinomethyl, 4-thiamorpholinomethyl, piperazin-1-ylmethyl, 4-methylpiperazin-1-ylmethyl, 4-ethylpiperazin-1-ylmethyl, 4-propylpiperazin-1-ylmethyl, 4-isopropylpiperazin-1-ylmethyl, 4-acetylpiperazin-1-ylmethyl and 4-methylhomopiperazin-1-ylmethyl;

or a pharmaceutically-acceptable salt thereof;
except that N-[5-(3-dimethylaminobenzamido)-2-methylphenyl]-4-hydroxybenzamide is excluded.

A more preferred group of novel compounds according to this aspect of the invention is an amide derivative of the Formula I
wherein $(R^1)_m$ is 3,4-dimethoxy or 3,4,5-trimethoxy;
p is 0;
R^3 is methyl;
q is 0; and
R^4 is phenyl which is substituted at the 3-position with a substituent selected from dimethylamino, morpholino, morpholinomethyl, piperazin-1-ylmethyl and 4-methylpiperazin-1-ylmethyl;
or a pharmaceutically-acceptable salt thereof.

A particular novel compound of this aspect of the present invention is:
N-[2-methyl-5-(3-morpholinobenzamido)phenyl]-3,4,5-trimethoxybenzamide,
and pharmaceutically-acceptable salts thereof.

In a further aspect of the present invention there is provided a group of novel compounds of the Formula I wherein R^1 is a basic substituent located at the 3- and/or 4-positions. This group of compounds possesses improved TNFα inhibitory potency in one or both of the PBMC and Human Whole Blood tests described hereinafter.

A particular group of novel compounds according to this aspect of the invention is an amide derivative of the Formula I
wherein R^1 is amino, C_{1-6}alkylamino, di-(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, heteroaryl, heteroarylC_{1-6}alkyl, heterocyclyl or heterocyclylC_{1-6}alkyl;
m is 1 with the R^1 group located at the 3-position or m is 2 with the R^1 groups, which may be the same or different, located at the 3- and 4-positions;
p is 0;
R^3 is methyl;
q is 0; and
R^4 is phenyl which is optionally substituted with 1 or 2 substituents, which may be the same or different, selected from hydroxy, C_{1-6}alkoxy, carboxy, C_{1-6}alkoxycarbonyl, cyano, C_{1-6}alkyl,

halo and trifluoromethyl;
or a pharmaceutically-acceptable salt thereof.

A preferred group of novel compounds according to this aspect of the invention is an amide derivative of the Formula I
wherein R^1 is amino, methylamino, dimethylamino, aminomethyl, pyrrolidin-1-yl, piperidino, morpholino, 4-thiamorpholino, piperazin-1-yl, 4-methylpiperazin-1-yl, 4-methylhomopiperazin-1-yl, pyrrolidin-1-ylmethyl, piperidinomethyl, 4-carbamoylpiperidin-1-ylmethyl, morpholinomethyl, 4-thiamorpholinomethyl, piperazin-1-ylmethyl, 4-methylpiperazin-1-ylmethyl, 4-ethylpiperazin-1-ylmethyl, 4-propylpiperazin-1-ylmethyl, 4-isopropylpiperazin-1-ylmethyl, 4-acetylpiperazin-1-ylmethyl or 4-methylhomopiperazin-1-ylmethyl;
m is 1 with the R^1 group located at the 3- or 4-position;
p is 0;
R^3 is methyl;
q is 0; and
R^4 is phenyl which is optionally substituted with 1 or 2 substituents, which may be the same or different, selected from hydroxy, methoxy, ethoxy, carboxy, methoxycarbonyl, cyano, methyl, fluoro, chloro and trifluoromethyl;
or a pharmaceutically-acceptable salt thereof.

A more preferred group of novel compounds according to this aspect of the invention is an amide derivative of the Formula I
wherein R^1 is morpholino, morpholinomethyl, piperazin-1-ylmethyl or 4-methylpiperazin-1-ylmethyl;
m is 1 with the R^1 group located at the 3-position;
p is 0;
R^3 is methyl;
q is 0; and
R^4 is phenyl which is optionally substituted with 1 or 2 substituents, which may be the same or different, selected from methoxy, ethoxy, cyano, fluoro, chloro and trifluoromethyl;
or a pharmaceutically-acceptable salt thereof.

Particular novel compounds of this aspect of the present invention are:

N-(5-benzamido-2-methylphenyl)-3-(piperazin-1-yl)methylbenzamide,
N-(5-benzamido-2-methylphenyl)-3-(4-methylpiperazin-1-yl)methylbenzamide,
N-[2-methyl-5-(3-trifluoromethylbenzamido)phenyl]-3-(4-methylpiperazin-1-yl)methylbenzamide,
N-[5-(3-chlorobenzamido)-2-methylphenyl]-3-(4-methylpiperazin-1-yl)methylbenzamide,
N-[5-(2-methoxybenzamido)-2-methylphenyl]-3-(4-methylpiperazin-1-yl)methylbenzamide and N-[5-(3-ethoxybenzamido)-2-methylphenyl]-3-(4-methylpiperazin-1-yl)methylbenzamide;
and pharmaceutically-acceptable salts thereof.

In yet another aspect of the present invention there is provided a group of novel compounds of the Formula I wherein $(R^1)_m$ represents a basic substituent located at the 3- and/or 4-positions and R^4 is phenyl which also bears a basic substituent located at the 3- and/or 4-positions. This group of compounds possesses improved TNFα inhibitory potency in one or both of the PBMC and Human Whole Blood tests described hereinafter.

A particular group of novel compounds according to this aspect of the invention is an amide derivative of the Formula I

wherein R^1 is amino, C_{1-6}alkylamino, di-(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, heteroaryl, heteroarylC_{1-6}alkyl, heterocyclyl or heterocyclylC_{1-6}alkyl;

m is 1 with the R^1 group located at the 3-position or m is 2 with the R^1 groups, which may be the same or different, located at the 3- and 4-positions;

p is 0;

R^3 is methyl;

q is 0; and

R^4 is phenyl which is substituted with 1 or 2 substituents selected from amino, C_{1-6}alkylamino, di-(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, heteroaryl, heteroarylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl, and when there is 1 substituent it is located at the 3-position and when there are 2 substituents, which may be the same or different, they are located at the 3- and 4-positions;

or a pharmaceutically-acceptable salt thereof.

A preferred group of novel compounds according to this aspect of the invention is an amide derivative of the Formula I

wherein R^1 is amino, methylamino, dimethylamino, aminomethyl, pyrrolidin-1-yl, piperidino, morpholino, 4-thiamorpholino, piperazin-1-yl, 4-methylpiperazin-1-yl, 4-methylhomopiperazin-1-yl, pyrrolidin-1-ylmethyl, piperidinomethyl, 4-carbamoylpiperidin-1-ylmethyl, morpholinomethyl, 4-thiamorpholinomethyl, piperazin-1-ylmethyl, 4-methylpiperazin-1-ylmethyl, 4-ethylpiperazin-1-ylmethyl, 4-propylpiperazin-1-ylmethyl, 4-isopropylpiperazin-1-ylmethyl, 4-acetylpiperazin-1-ylmethyl or 4-methylhomopiperazin-1-ylmethyl;

m is 1 with the R^1 group located at the 3- or 4-position;

p is 0;

R^3 is methyl;

q is 0; and

R^4 is phenyl which is substituted at the 3- or 4-position with a substituent selected from amino, methylamino, dimethylamino, aminomethyl, pyrrolidin-1-yl, piperidino, morpholino, 4-thiamorpholino, piperazin-1-yl, 4-methylpiperazin-1-yl, 4-methylhomopiperazin-1-yl, pyrrolidin-1-ylmethyl, piperidinomethyl, 4-carbamoylpiperidin-1-ylmethyl, morpholinomethyl, 4-thiamorpholinomethyl, piperazin-1-ylmethyl, 4-methylpiperazin-1-ylmethyl, 4-ethylpiperazin-1-ylmethyl, 4-propylpiperazin-1-ylmethyl, 4-isopropylpiperazin-1-ylmethyl, 4-acetylpiperazin-1-ylmethyl and 4-methylhomopiperazin-1-ylmethyl;

or a pharmaceutically-acceptable salt thereof.

A more preferred group of novel compounds according to this aspect of the invention is an amide derivative of the Formula I

wherein R^1 is morpholino, morpholinomethyl, piperazin-1-ylmethyl or 4-methylpiperazin-1-ylmethyl;

m is 1 with the R^1 group located at the 3-position;

p is 0;

R^3 is methyl;

q is 0; and

R^4 is phenyl which is substituted at the 3-position with a substituent selected from dimethylamino, morpholino, morpholinomethyl, piperazin-1-ylmethyl and 4-methylpiperazin-1-ylmethyl;

or a pharmaceutically-acceptable salt thereof.

Particular novel compounds of this aspect of the present invention are:
N-[2-methyl-5-(3-morpholinobenzamido)phenyl]-3-morpholinobenzamide and
N-[2-methyl-5-(3-morpholinobenzamido)phenyl]-3-(4-methylpiperazin-1-yl)methylbenzamide;
and pharmaceutically-acceptable salts thereof.

A suitable pharmaceutically-acceptable salt of a compound of the Formula I is, for example, an acid-addition salt of a compound of the Formula I which is sufficiently basic, for example an acid-addition salt with an inorganic or organic acid such as hydrochloric, hydrobromic, sulphuric, trifluoroacetic, citric or maleic acid; or, for example a salt of a compound of the Formula I which is sufficiently acidic, for example an alkali or alkaline earth metal salt such as a calcium or magnesium salt, or an ammonium salt, or a salt with an organic base such as methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

Various forms of prodrugs are known in the art. For examples of such prodrug derivatives, see:

a) Design of Prodrugs, edited by H. Bundgaard, (Elsevier, 1985) and Methods in Enzymology, Vol. 42, p. 309-396, edited by K. Widder, *et al.* (Academic Press, 1985);

b) A Textbook of Drug Design and Development, edited by Krogsgaard-Larsen and H. Bundgaard, Chapter 5 "Design and Application of Prodrugs", by H. Bundgaard p. 113-191 (1991);

c) H. Bundgaard, Advanced Drug Delivery Reviews, 8, 1-38 (1992);

d) H. Bundgaard, *et al.*, Journal of Pharmaceutical Sciences, 77, 285 (1988); and

e) N. Kakeya, *et al.*, Chem Pharm Bull, 32, 692 (1984).

Examples of such pro-drugs may be used to form in vivo cleavable esters of a compound of the Formula I. An in vivo cleavable ester of a compound of the Formula I containing a carboxy group is, for example, a pharmaceutically-acceptable ester which is cleaved in the human or animal body to produce the parent acid. Suitable pharmaceutically-acceptable esters for carboxy include C_{1-6}alkoxymethyl esters, for example methoxymethyl; C_{1-6}alkanoyloxymethyl esters, for example pivaloyloxymethyl; phthalidyl esters; C_{3-8}cycloalkoxycarbonyloxyC_{1-6}alkyl esters, for example 1-cyclohexylcarbonyloxyethyl;

1,3-dioxolan-2-ylmethyl esters, for example 5-methyl-1,3-dioxolan-2-ylmethyl; and C_{1-6}alkoxycarbonyloxyethyl esters, for example 1-methoxycarbonyloxyethyl; and may be formed at any carboxy group in the compounds of this invention.

In order to use a compound of the Formula I, or a pharmaceutically-acceptable salt or in vivo cleavable ester thereof, for the therapeutic treatment (including prophylactic treatment) of mammals including humans, it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

According to this aspect of the invention there is provided a pharmaceutical composition which comprises an amide derivative of the Formula I, or a pharmaceutically-acceptable salt or in vivo cleavable ester thereof, as defined hereinbefore in association with a pharmaceutically-acceptable diluent or carrier.

The compositions of the invention may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions), for administration by inhalation (for example as a finely divided powder or a liquid aerosol), for administration by insufflation (for example as a finely divided powder) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous, intramuscular or intramuscular dosing or as a suppository for rectal dosing).

The compositions of the invention may be obtained by conventional procedures using conventional pharmaceutical excipients, well known in the art. Thus, compositions intended for oral use may contain, for example, one or more colouring, sweetening, flavouring and/or preservative agents.

Suitable pharmaceutically-acceptable excipients for a tablet formulation include, for example, inert diluents such as lactose, sodium carbonate, calcium phosphate or calcium carbonate, granulating and disintegrating agents such as corn starch or algenic acid; binding agents such as starch; lubricating agents such as magnesium stearate, stearic acid or talc; preservative agents such as ethyl or propyl p-hydroxybenzoate, and anti-oxidants, such as ascorbic acid. Tablet formulations may be uncoated or coated either to modify their disintegration and the subsequent absorption of the active ingredient within the gastrointestinal tract, or to improve their stability and/or appearance, in either case, using

conventional coating agents and procedures well known in the art.

Compositions for oral use may be in the form of hard gelatin capsules in which the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules in which the active ingredient is mixed with water or an oil such as peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions generally contain the active ingredient in finely powdered form together with one or more suspending agents, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents such as lecithin or condensation products of an alkylene oxide with fatty acids (for example polyoxethylene stearate), or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives (such as ethyl or propyl p-hydroxybenzoate, anti-oxidants (such as ascorbic acid), colouring agents, flavouring agents, and/or sweetening agents (such as sucrose, saccharine or aspartame).

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil (such as arachis oil, olive oil, sesame oil or coconut oil) or in a mineral oil (such as liquid paraffin). The oily suspensions may also contain a thickening agent such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set out above, and flavouring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water generally contain the active ingredient together with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients such as sweetening, flavouring and colouring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-

water emulsions. The oily phase may be a vegetable oil, such as olive oil or arachis oil, or a mineral oil, such as for example liquid paraffin or a mixture of any of these. Suitable emulsifying agents may be, for example, naturally-occurring gums such as gum acacia or gum tragacanth, naturally-occurring phosphatides such as soya bean, lecithin, an esters or partial esters derived from fatty acids and hexitol anhydrides (for example sorbitan monooleate) and condensation products of the said partial esters with ethylene oxide such as polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening, flavouring and preservative agents.

Syrups and elixirs may be formulated with sweetening agents such as glycerol, propylene glycol, sorbitol, aspartame or sucrose, and may also contain a demulcent, preservative, flavouring and/or colouring agent.

The pharmaceutical compositions may also be in the form of a sterile injectable aqueous or oily suspension, which may be formulated according to known procedures using one or more of the appropriate dispersing or wetting agents and suspending agents, which have been mentioned above. A sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example a solution in 1,3-butanediol.

Suppository formulations may be prepared by mixing the active ingredient with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Suitable excipients include, for example, cocoa butter and polyethylene glycols.

Topical formulations, such as creams, ointments, gels and aqueous or oily solutions or suspensions, may generally be obtained by formulating an active ingredient with a conventional, topically acceptable, vehicle or diluent using conventional procedures well known in the art.

Compositions for administration by insufflation may be in the form of a finely divided powder containing particles of average diameter of, for example, 30μm or much less, the powder itself comprising either active ingredient alone or diluted with one or more physiologically acceptable carriers such as lactose. The powder for insufflation is then conveniently retained in a capsule containing, for example, 1 to 50mg of active ingredient for use with a turbo-inhaler device, such as is used for insufflation of the known agent sodium

cromoglycate.

Compositions for administration by inhalation may be in the form of a conventional pressurised aerosol arranged to dispense the active ingredient either as an aerosol containing finely divided solid or liquid droplets. Conventional aerosol propellants such as volatile fluorinated hydrocarbons or hydrocarbons may be used and the aerosol device is conveniently arranged to dispense a metered quantity of active ingredient.

For further information on Formulation the reader is referred to Chapter 25.2 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

The amount of active ingredient that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treated and the particular route of administration. For example, a formulation intended for oral administration to humans will generally contain, for example, from 0.5 mg to 2 g of active agent compounded with an appropriate and convenient amount of excipients which may vary from about 5 to about 98 percent by weight of the total composition. Dosage unit forms will generally contain about 1 mg to about 500 mg of an active ingredient. For further information on Routes of Administration and Dosage Regimes the reader is referred to Chapter 25.3 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

The size of the dose for therapeutic or prophylactic purposes of a compound of the Formula I will naturally vary according to the nature and severity of the conditions, the age and sex of the animal or patient and the route of administration, according to well known principles of medicine.

In using a compound of the Formula I for therapeutic or prophylactic purposes it will generally be administered so that a daily dose in the range, for example, 0.5 mg to 75 mg per kg body weight, preferably 0.5 mg to 40 mg per kg body weight, is received, given if required in divided doses. In general lower doses will be administered when a parenteral route is employed. Thus, for example, for intravenous administration, a dose in the range, for example, 0.5 mg to 30 mg per kg body weight will generally be used. Similarly, for administration by inhalation, a dose in the range, for example, 0.5 mg to 25 mg per kg body weight will be used. Oral administration is however preferred, particularly in tablet form.

Typically, unit dosage forms will contain about 1 mg to 500 mg of a compound of this invention.

The compounds of this invention may be used in combination with other drugs and therapies used in the treatment of disease states which would benefit from the inhibition of cytokines, in particular TNF and IL-1. For example, the compounds of the Formula I could be used in combination with drugs and therapies used in the treatment of rheumatoid arthritis, asthma, irritable bowel disease, multiple sclerosis, AIDS, septic shock, ischaemic heart disease, psoriasis and the other disease states mentioned earlier in this specification.

For example, by virtue of their ability to inhibit cytokines, the compounds of the Formula I are of value in the treatment of certain inflammatory and non-inflammatory diseases which are currently treated with a cyclooxygenase-inhibitory non-steroidal anti-inflammatory drug (NSAID) such as indomethacin, ketorolac, acetylsalicyclic acid, ibuprofen, sulindac, tolmetin and piroxicam. Co-administration of a compound of the Formula I with a NSAID can result in a reduction of the quantity of the latter agent needed to produce a therapeutic effect. Thereby the likelihood of adverse side-effects from the NSAID such as gastrointestinal effects are reduced. Thus according to a further feature of the invention there is provided a pharmaceutical composition which comprises a compound of the Formula I, or a pharmaceutically-acceptable salt or in vivo cleavable ester thereof, in conjunction or admixture with a cyclooxygenase inhibitory non-steroidal anti-inflammatory agent, and a pharmaceutically-acceptable diluent or carrier.

The compounds of the invention may also be used with anti-inflammatory agents such as an inhibitor of the enzyme 5-lipoxygenase (such as those disclosed in European Patent Applications Nos. 0351194, 0375368, 0375404, 0375452, 0375457, 0381375, 0385662, 0385663, 0385679, 0385680).

The compounds of the Formula I may also be used in the treatment of conditions such as rheumatoid arthritis in combination with antiarthritic agents such as gold, methotrexate, steroids and penicillinamine, and in conditions such as osteoarthritis in combination with steroids.

The compounds of the present invention may also be administered in degradative diseases, for example osteoarthritis, with chondroprotective, anti-degradative and/or

reparative agents such as Diacerhein, hyaluronic acid formulations such as Hyalan, Rumalon, Arteparon and glucosamine salts such as Antril.

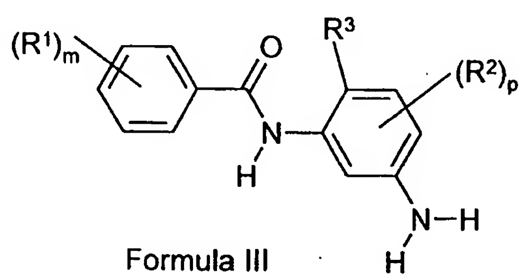
The compounds of the Formula I may be be used in the treatment of asthma in combination with antiasthmatic agents such as bronchodilators and leukotriene antagonists.

If formulated as a fixed dose such combination products employ the compounds of this invention within the dosage range described herein and the other pharmaceutically-active agent within its approved dosage range. Sequential use is contemplated when a combination formulation is inappropriate.

Although the compounds of the Formula I are primarily of value as therapeutic agents for use in warm-blooded animals (including man), they are also useful whenever it is required to inhibit the effects of cytokines. Thus, they are useful as pharmacological standards for use in the development of new biological tests and in the search for new pharmacological agents.

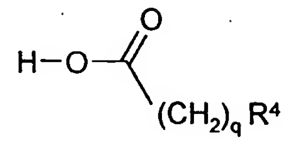
An amide derivative of the Formula I, or a pharmaceutically-acceptable salt or in vivo cleavable ester thereof, may be prepared by any process known to be applicable to the preparation of chemically-related compounds. Suitable processes are illustrated by, for example, those used in J. Med. Chem., 1996, 39, 3343-3356. Such processes, when used to prepare a novel amide derivative of the Formula I are provided as a further feature of the invention and are illustrated by the following representative process variants in which, unless otherwise stated, R^1, R^2, R^3, R^4, m, p and q have any of the meanings defined hereinbefore. Necessary starting materials may be obtained by standard procedures of organic chemistry. The preparation of such starting materials is described in conjunction with the following representative process variants and within the accompanying Examples. Alternatively necessary starting materials are obtainable by analogous procedures to those illustrated which are within the ordinary skill of an organic chemist.

(a) A compound of the Formula I, or a pharmaceutically-acceptable salt or in vivo cleavable ester thereof, may be prepared by reacting a compound of the Formula III



Formula III

with a compound of the Formula IV



Formula IV

or an activated derivative thereof, under standard amide bond forming conditions, wherein variable groups are as hereinbefore defined and wherein any functional group is protected, if necessary, and:

i. removing any protecting groups;

ii. optionally forming a pharmaceutically-acceptable salt or in vivo cleavable ester.

A suitable activated derivative of an acid of the Formula IV is, for example, an acyl halide, for example an acyl chloride formed by the reaction of the acid and an inorganic acid chloride, for example thionyl chloride; a mixed anhydride, for example an anhydride formed by the reaction of the acid and a chloroformate such as isobutyl chloroformate; an active ester, for example an ester formed by the reaction of the acid and a phenol such as pentafluorophenol, an ester such as pentafluorophenyl trifluoroacetate or an alcohol such as N-hydroxybenzotriazole; an acyl azide, for example an azide formed by the reaction of the acid and an azide such as diphenylphosphoryl azide; an acyl cyanide, for example a cyanide formed by the reaction of an acid and a cyanide such as diethylphosphoryl cyanide; or the product of the reaction of the acid and a carbodiimide such as dicyclohexylcarbodiimide.

The reaction is preferably carried out in the presence of a suitable base such as, for example, an alkali or alkaline earth metal carbonate, alkoxide, hydroxide or hydride, for example sodium carbonate, potassium carbonate, sodium ethoxide, potassium butoxide, sodium hydroxide, potassium hydroxide, sodium hydride or potassium hydride, or an organometallic base such as an alkyl-lithium, for example n-butyl-lithium, or a dialkylamino-lithium, for example lithium di-isopropylamide, or, for example, an organic amine base such as, for example, pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, morpholine or diazabicyclo[5.4.0]undec-7-ene. The reaction is also preferably carried out in a suitable inert solvent or diluent, for example tetrahydrofuran, 1,2-dimethoxyethane, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidin-2-one, dimethylsulphoxide or acetone, and at a temperature in the range,

for example, -78° to 150°C, conveniently at or near ambient temperature.

Typically a carbodiimide coupling reagent is used in the presence of an organic solvent (preferably an anhydrous polar aprotic organic solvent) at a non-extreme temperature, for example in the region -10 to 40°C, typically at ambient temperature of about 20°C.

Protecting groups may in general be chosen from any of the groups described in the literature or known to the skilled chemist as appropriate for the protection of the group in question and may be introduced by conventional methods. Protecting groups may be removed by any convenient method as described in the literature or known to the skilled chemist as appropriate for the removal of the protecting group in question, such methods being chosen so as to effect removal of the protecting group with minimum disturbance of groups elsewhere in the molecule.

Specific examples of protecting groups are given below for the sake of convenience, in which "lower", as in, for example, lower alkyl, signifies that the group to which it is applied preferably has 1-4 carbon atoms. It will be understood that these examples are not exhaustive. Where specific examples of methods for the removal of protecting groups are given below these are similarly not exhaustive. The use of protecting groups and methods of deprotection not specifically mentioned is of course within the scope of the invention.

A carboxy protecting group may be the residue of an ester-forming aliphatic or arylaliphatic alcohol or of an ester-forming silanol (the said alcohol or silanol preferably containing 1-20 carbon atoms).

Examples of carboxy protecting groups include straight or branched chain C_{1-12}alkyl groups (for example isopropyl, tert-butyl); lower alkoxy lower alkyl groups (for example methoxymethyl, ethoxymethyl, isobutoxymethyl); lower aliphatic acyloxy lower alkyl groups, (for example acetoxymethyl, propionyloxymethyl, butyryloxymethyl, pivaloyloxymethyl); lower alkoxycarbonyloxy lower alkyl groups (for example 1-methoxycarbonyloxyethyl, 1-ethoxycarbonyloxyethyl); aryl lower alkyl groups (for example benzyl, p-methoxybenzyl, o-nitrobenzyl, p-nitrobenzyl, benzhydryl and phthalidyl); tri(lower alkyl)silyl groups (for example trimethylsilyl and tert-butyldimethylsilyl); tri(lower alkyl)silyl lower alkyl groups (for example trimethylsilylethyl); and C_{2-6}alkenyl groups (for example allyl and vinylethyl).

Methods particularly appropriate for the removal of carboxyl protecting groups include for example acid-, base-, metal- or enzymically-catalysed hydrolysis.

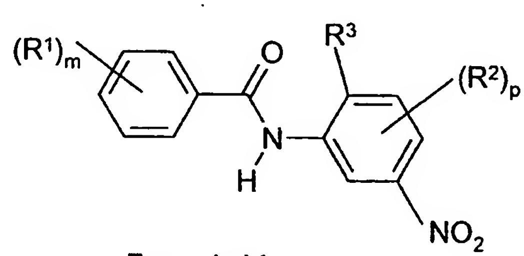
Examples of hydroxy protecting groups include lower alkyl groups (for example tert-butyl), lower alkenyl groups (for example allyl); lower alkanoyl groups (for example acetyl); lower alkoxycarbonyl groups (for example tert-butoxycarbonyl); lower alkenyloxycarbonyl groups (for example allyloxycarbonyl); aryl lower alkoxycarbonyl groups (for example benzoyloxycarbonyl, p-methoxybenzyloxycarbonyl, o-nitrobenzyloxycarbonyl, p-nitrobenzyloxycarbonyl); tri lower alkylsilyl (for example trimethylsilyl, tert-butyldimethylsilyl) and aryl lower alkyl (for example benzyl) groups.

Examples of amino protecting groups include formyl, aralkyl groups (for example benzyl and substituted benzyl, p-methoxybenzyl, nitrobenzyl and 2,4-dimethoxybenzyl, and triphenylmethyl); di-p-anisylmethyl and furylmethyl groups; lower alkoxycarbonyl (for example tert-butoxycarbonyl); lower alkenyloxycarbonyl (for example allyloxycarbonyl); aryl lower alkoxycarbonyl groups (for example benzyloxycarbonyl, p-methoxybenzyloxycarbonyl, o-nitrobenzyloxycarbonyl, p-nitrobenzyloxycarbonyl; trialkylsilyl (for example trimethylsilyl and tert-butyldimethylsilyl); alkylidene (for example methylidene); benzylidene and substituted benzylidene groups.

Methods appropriate for removal of hydroxy and amino protecting groups include, for example, acid-, base-, metal- or enzymically-catalysed hydrolysis for groups such as p-nitrobenzyloxycarbonyl, hydrogenation for groups such as benzyl and photolytically for groups such as o-nitrobenzyloxycarbonyl.

The reader is referred to Advanced Organic Chemistry, 4th Edition, by Jerry March, published by John Wiley & Sons 1992, for general guidance on reaction conditions and reagents. The reader is referred to Protective Groups in Organic Synthesis, 2nd Edition, by Green *et al.*, published by John Wiley & Sons for general guidance on protecting groups.

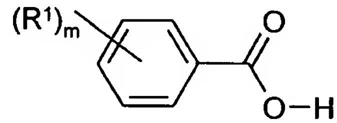
The compound of Formula III may be prepared by reduction of the corresponding nitro compound of Formula V.



Formula V

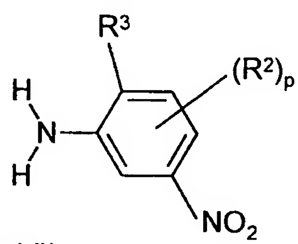
Typical reaction conditions include the use of ammonium formate in the presence of a catalyst (for example palladium-on-carbon) in the presence of an organic solvent (preferably a polar protic solvent), preferably with heating, for example to about 60°C. Any functional groups are protected and deprotected as necessary.

The compound of Formula V may be prepared by reaction of a compound of Formula VI, or an activated derivative thereof as defined hereinbefore,



Formula VI

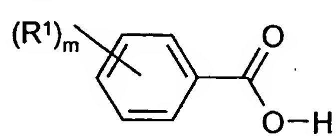
with a compound of Formula VII under suitable amide bond forming conditions.



Formula VII

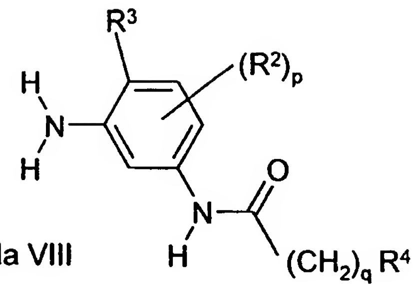
Typical conditions include activating the carboxy group of the compound of Formula VI for example by treatment with a halo reagent (for example oxalyl chloride) to form an acyl halide in an organic solvent at ambient temperature, then reacting the activated compound with the compound of Formula VII. Any functional groups are protected and deprotected as necessary.

(b) A compound of the Formula I, or a pharmaceutically-acceptable salt or in vivo cleavable ester thereof, may be prepared by reacting an acid of the Formula VI



Formula VI

or an activated derivative thereof as defined hereinbefore, with an aniline of the Formula VIII



Formula VIII

under standard amide bond forming conditions, wherein variable groups are as hereinbefore defined and wherein any functional group is protected, if necessary, and:

i. removing any protecting groups;

ii. optionally forming a pharmaceutically-acceptable salt or in vivo cleavable ester.

The aniline of Formula VIII may be prepared by reduction of the corresponding nitro compound using convention procedures as defined hereinbefore or as illustrated in the Examples.

(c) A compound of the Formula I wherein R^1 or a substituent on R^4 is heterocyclylC_{1-6}alkyl may be prepared by the reaction of a compound of the Formula I wherein R^1 or a substituent on R^4 is a group of the formula -C_{1-6}alkyl-Z wherein Z is a displaceable group with a heterocyclyl compound.

A suitable displaceable group Z is, for example, a halogeno group such as fluoro, chloro or bromo, a C_{1-6}alkanesulphonyloxy group such as methanesulphonyloxy or an arylsulphonyloxy group such as 4-toluenesulphonyloxy.

The reaction is conveniently carried out in the presence of a suitable base as defined hereinbefore and in the presence of a suitable inert diluent or carrier as defined hereinbefore.

(d) A compound of the Formula I wherein R^1, R^2 or a substituent on R^4 is carboxy may be prepared by the cleavage of a compound of the Formula I wherein R^1, R^2 or a substituent on R^4 is C_{1-6}alkoxycarbonyl.

The cleavage reaction may conveniently be carried out by any of the many procedures known in the art for such a transformation. The reaction may be carried out, for example, by hydrolysis under acidic or basic conditions. A suitable base is, for example, an alkali metal, alkaline earth metal or ammonium carbonate or hydroxide, for example sodium carbonate, potassium carbonate, sodium hydroxide, potassium hydroxide or ammonium hydroxide. The reaction is preferably carried out in the presence of water and a suitable solvent or diluent

such as methanol or ethanol. The reaction is conveniently carried out at a temperature in the range 10 to 150°C, preferably at or near ambient temperature.

(e) A compound of the Formula I wherein R^1, R^2 or a substituent on R^4 is hydroxy may be prepared by cleavage of a compound of the Formula I wherein R^1, R^2 or a substituent on R^4 is benzyloxy or substituted benzyloxy.

Typical reaction conditions include the hydrogenolysis of a benzyloxy group in the presence of a suitable catalyst such as palladium-on-carbon.

(f) A compound of the Formula I wherein R^1, R^2 or a substituent on R^4 is amino may be prepared by the reduction of a compound of the Formula I wherein R^1, R^2 or a substituent on R^4 is nitro.

Typical reaction conditions include the use of hydrogen or of ammonium formate in the presence of a suitable catalyst such as palladium-on-carbon.

(g) A compound of the Formula I wherein R^1, R^2 or a substituent on R^4 is C_{1-6}alkanoylamino may be prepared by the acylation of a compound of the Formula I wherein R^1, R^2 or a substituent on R^4 is amino.

A suitable acylating agent is, for example, any agent known in the art for the acylation of amino to acylamino, for example an acyl halide, for example a C_{1-6}alkanoyl chloride or bromide, conveniently in the presence of a suitable base, as defined hereinbefore, an alkanoic acid anhydride or mixed anhydride, for example a C_{1-6}alkanoic acid anhydride such as acetic anhydride or the mixed anhydride formed by the reaction of an alkanoic acid and a C_{1-6}alkoxycarbonyl halide, for example a C_{1-6}alkoxycarbonyl chloride, in the presence of a suitable base as defined hereinbefore. In general the acylation is carried out in a suitable inert solvent or diluent as defined hereinbefore and at a temperature, in the range, for example, -30 to 120°C, conveniently at or near ambient temperature.

The following biological assays and Examples serve to illustrate the present invention.

Biological Assays

The following assays can be used to measure the p38 kinase-inhibitory, the TNF-inhibitory and anti-arthritic effects of the compounds of the present invention:

In vitro enzyme assay

The ability of compounds of the invention to inhibit the enzyme p38 kinase was assessed. Activity of particular test compounds against each of the p38α and p38β isoforms of the enzyme was determined.

Human recombinant MKK6 (GenBank Accesion Number G1209672) was isolated from Image clone 45578 (Genomics, 1996, 33, 151) and utilised to produce protein in the form of a GST fusion protein in a pGEX vector using analogous procedures to those disclosed by J. Han et al., Journal of Biological Chemistry, 1996, 271, 2886-2891. p38α (GenBank Accession Number G529039) and p38β (GenBank Accession Number G1469305) were isolated by PCR amplification of human lymphoblastoid cDNA (GenBank Accession Number GM1416) and human foetal brain cDNA [synthesised from mRNA (Clontech, catalogue no. 6525-1) using a Gibco superscript cDNA synthesis kit] respectively using oligonucleotides designed for the 5′ and 3′ ends of the human p38α and p38β genes using analogous procedures to those described by J.Han et al., Biochimica et Biophysica Acta, 1995, 1265, 224-227 and Y. Jiang et al., Journal of Biological Chemistry, 1996, 271, 17920-17926.

Both p38 protein isoforms were expressed in e coli in PET vectors. Human recombinant p38α and p38β isoforms were produced as 5′ c-myc, 6His tagged proteins. Both MKK6 and the p38 proteins were purified using standard protocols: the GST MKK6 was purified using a glutathione sepharose column and the p38 proteins were purified using nickel chelate columns.

The p38 enzymes were activated prior to use by incubation with MKK6 for 3 hours at 30°C. The unactivated coli-expressed MKK6 retained sufficient activity to fully activate both isoforms of p38. The activation incubate comprised p38α (10μl of 10mg/ml) or p38β (10μl of 5mg/ml) together with MKK6 (10μl of 1mg/ml), 'Kinase buffer' [100μl; pH 7.4 buffer comprising Tris (50mM), EGTA (0.1mM), sodium orthovanadate (0.1mM) and β-mercaptoethanol (0.1%)] and MgATP (30μl of 50mM $Mg(OCOCH_3)_2$ and 0.5mM ATP). This produced enough activated p38 enzyme for 3 Microtiter plates.

Test compounds were solubilised in DMSO and 10μl of a 1:10 diluted sample in 'Kinase Buffer' was added to a well in a Microtiter plate. For single dose testing, the compounds were tested at 10μM. 'Kinase Assay Mix' [30μl; comprising Myelin Basic

Protein (Gibco BRL cat. no. 1322B-010; 1ml of a 3.33mg/ml solution in water), activated p38 enzyme (50μl) and 'Kinase Buffer' (2ml)] was then added followed by 'Labelled ATP' [10μl; comprising 50μM ATP, 0.1μCi ^{33}P ATP (Amersham International cat. no. BF1000) and 50mM $Mg(OCOCH_3)_2$]. The plates were incubated at room temperature with gentle agitation. Plates containing p38α were incubated for 90min and plates containing p38β were incubated for 45min. Incubation was stopped by the addition of 50μl of 20% trichloroacetic acid (TCA). The precipitated protein was phosphorylated by p38 kinase and test compounds were assessed for their ability to inhibit this phosphorylation. The plates were filtered using a Canberra Packard Unifilter and washed with 2% TCA, dried overnight and counted on a Top Count scintillation counter.

Test compounds were tested initially at a single dose and active compounds were retested to allow IC_{50} values to be determined.

In vitro cell-based assays

(i) **PBMC**

The ability of compounds of this invention to inhibit TNFα production was assessed by using human peripheral blood mononuclear cells which synthesise and secrete TNFα when stimulated with lipopolysaccharide.

Peripheral blood mononuclear cells (PBMC) were isolated from heparinised (10units/ml heparin) human blood by density centrifugation (Lymphoprep™ ; Nycomed). Mononuclear cells were resuspended in culture medium [RPMI 1640 medium (Gibco) supplemented with 50 units/ml penicillin, 50μg/ml streptomycin, 2mM glutamine and 1% heat-inactivated human AB serum (Sigma H-1513)]. Compounds were solubilised in DMSO at a concentration of 50mM, diluted 1:100 in culture medium and subsequently serial dilutions were made in culture medium containing 1% DMSO. PBMCs (2.4×10^5 cells in 160μl culture medium) were incubated with 20μl of varying concentrations of test compound (triplicate cultures) or 20μl culture medium containing 1% DMSO (control wells) for 30 minutes at 37°C in a humidified (5%CO_2/95% air) incubator (Falcon 3072 ; 96 well flat-bottom tissue culture plates). 20μl lipopolysaccharide [LPS E.Coli 0111:B4 (Sigma L-4130), final concentration 10μg/ml] solubilised in culture medium was added to appropriate wells. 20μl culture medium was added to "medium alone" control wells. Six "LPS alone" and four "medium alone" controls were included on each 96 well plate. Varying concentrations of

a known TNFα inhibitor were included in each test, i.e. an inhibitor of the PDE Type IV enzyme (for example see Semmler, J. Wachtel. H and Endres, S., Int. J. Immunopharmac. (1993), 15(3), 409-413) or an inhibitor of proTNFα convertase (for example, see McGeehan, G. M. et al. Nature (1994) 370, 558-561). Plates were incubated for 7 hours at 37°C (humidified incubator) after which 100μl of the supernatant was removed from each well and stored at -70°C (96 well round-bottom plates; Corning 25850). TNFα levels were determined in each sample using a human TNFα ELISA (see WO92/10190 and Current Protocols in Molecular Biology, vol 2 by Frederick M. Ausbel et al., John Wiley and Sons Inc.).

% inhibition =

$$\frac{\text{(LPS alone control - medium alone control) - (test concentration - medium alone control)}}{\text{(LPS alone control - medium alone control)}} \times 100$$

(ii) **Human Whole Blood**

The ability of the compounds of this invention to inhibit TNFα production was also assessed in a human whole blood assay. Human whole blood secretes TNFα when stimulated with LPS. This property of blood forms the basis of an assay which is used as a secondary test for compounds which profile as active in the PBMC test.

Heparinised (10 units/ml) human blood was obtained from volunteers. 160μl whole blood were added to 96 well round-bottom plates (Corning 25850). Compounds were solubilised and serially diluted in RPMI 1640 medium (Gibco) supplemented with 50 units/ml penicillin, 50μg/ml streptomycin and 2mM glutamine, as detailed above. 20μl of each test concentration was added to appropriate wells (triplicate cultures). 20μl of RPMI 1640 medium supplemented with antibiotics and glutamine was added to control wells. Plates were incubated for 30 minutes at 37°C (humidified incubator), prior to addition of 20μl LPS (final concentration 10μg/ml). RPMI 1640 medium was added to control wells. Six "LPS alone" and four "medium alone" controls were included on each plate. A known TNFα synthesis/secretion inhibitor was included in each test. Plates were incubated for 6 hours at 37°C (humidified incubator). Plates were centrifuged (2000rpm for 10 minutes) and 100μl plasma removed and stored at -70°C (Corning 25850 plates). TNFα levels were measured by ELISA (see WO92/10190 and Current Protocols in Molecular Biology, vol 2 by Frederick M. Ausbel et al., John Wiley and Sons Inc.). The paired antibodies that were used in the ELIZA

were obtained from R&D Systems (catalogue nos. MAB610 anti-human TNFα coating antibody, BAF210 biotinylated anti-human TNFα detect antibody).

Ex vivo / In vivo assessment

The ability of the compounds of this invention as *ex vivo* TNFα inhibitors were assessed in the rat or mouse. Briefly, groups of male Wistar Alderley Park (AP) rats (180-210g) were dosed with compound (6 rats) or drug vehicle (10 rats) by the appropriate route, for example peroral (p.o.), intraperitoneal (i.p.) or subcutaneous (s.c.). Ninety minutes later rats were sacrificed using a rising concentration of CO_2 and bled out via the posterior vena cavae into 5 Units of sodium heparin/ml blood. Blood samples were immediately placed on ice and centrifuged at 2000 rpm for 10 min at 4°C and the harvested plasmas frozen at -20°C for subsequent assay of their effect on TNFα production by LPS-stimulated human blood. The rat plasma samples were thawed and 175μl of each sample was added to a set format pattern in a 96 well round bottom plate (Corning 25850). 50μl of heparinized human blood was then added to each well, mixed and the plate was incubated for 30 min at 37°C (humidified incubator). LPS (25μl; final concentration10μg/ml) was added to the wells and incubation continued for a further 5.5 hours. Control wells were incubated with 25μl of medium alone. Plates were then centrifuged for 10 min at 2000 rpm and 200μl of the supernatants were transferred to a 96 well plate and frozen at -20°C for subsequent analysis of TNF concentration by ELISA.

Data analysis by dedicated software calculates for each compound/dose:

$$\text{Percent inhibition of TNF}\alpha = \frac{\text{Mean TNF}\alpha\text{ (Controls) - Mean TNF}\alpha\text{ (Treated)}}{\text{Mean TNF}\alpha\text{ (Controls)}} \times 100$$

Alternatively, mice could be used instead of rats in the above procedure.

Test as anti-arthritic agent

Activity of a compound as an anti-arthritic agent was tested as follows. Acid soluble native type II collagen was shown by Trentham et al. [1] to be arthritogenic in rats; it caused polyarthritis when administered in Freunds incomplete adjuvant. This is now known as collagen-induced arthritis (CIA) and similar conditions can be induced in mice and primates. Recent studies have shown that anti-TNF monoclonal antibodies [2] and TNF receptor-IgG fusion proteins [3] ameliorate established CIA indicating that TNF plays a key role in the pathophysiology of CIA. Moreover, the remarkable efficacy reported for anti-TNF

monoclonal antibodies in recent rheumatoid arthritis clinical trials indicates that TNF plays a major role in this chronic inflammatory disease. Thus CIA in DBA/1 mice as described in references 2 and 3 is a tertiary model which can be used to demonstrate the anti-arthritic activity of a compound. Also see reference 4.

1. Trentham, D.E. et al., (1977) J. Exp. Med., 146, 857.
2. Williams, R.O. et al., (1992) Proc. Natl. Acad. Sci., 89, 9784.
3. Williams, R.O. et al., (1995) Immunology, 84, 433.
4 Badger, M. B. et al., (1996) The Journal of Pharmacology and Experimental Therapeutics, 279, 1453-1461.

Although the pharmacological properties of the compounds of the Formula I vary with structural change as expected, in general a compound of the Formula I gives over 30% inhibition of p38α and/or p38β at concentrations up to 10μM and over 30% inhibition in the PBMC test at concentrations up to 50μM. No physiologically unacceptable toxicity was observed at the effective dose for compounds tested of the present invention. By way of example :-

N-[5-(2-fluoro-6-chlorobenzamido-2-methylphenyl]-4-hydroxybenzamide [Example 9, Compound No. 12] has an IC_{50} of approximately 1.7μM against p38α and an IC_{50} of approximately 22μM in the PBMC test;

N-[5-(3-aminobenzamido)-2-methylphenyl]-3,4-dimethoxybenzamide [Example 13] has an IC_{50} of approximately 0.7μM against p38α and an IC_{50} of approximately 7μM in the PBMC test;

N-[5-(3-dimethylaminobenzamido)-2-methylphenyl]-3,4-dimethoxybenzamide [Example 9, Compound No. 7] has an IC_{50} of approximately 0.2μM against p38α and an IC_{50} of approximately 7μM in the PBMC test;

N-(5-benzamido-2-methylphenyl)-3-(4-methylpiperazin-1-yl)methylbenzamide, [Example 9, Compound No. 51] has an IC_{50} of approximately 0.7μM against p38α and an IC_{50} of approximately 3μM in the PBMC test;

N-[2-methyl-5-(3-morpholinobenzamido)phenyl]-3-morpholinobenzamide [Example 9, Compound No. 50] has an IC_{50} of approximately 0.04μM against p38α and an IC_{50} of approximately 1.5μM in the PBMC test;

N-[5-(3-cyclopentylpropionamido)-2-methylphenyl]-4-hydroxybenzamide has an IC_{50} of approximately 6μM against p38α; and

N-[5-(3-cyclohexylpropionamido)-2-methylphenyl]-4-hydroxybenzamide has an IC_{50} of approximately 0.4μM against p38α and an IC_{50} of approximately 7μM in the PBMC test.

The invention will now be illustrated in the following non-limiting Examples in which, unless otherwise stated:-

(i) operations were carried out at ambient temperature, i.e. in the range 17 to 25°C and under an atmosphere of an inert gas such as argon unless otherwise stated;

(ii) evaporations were carried out by rotary evaporation in vacuo and work-up procedures were carried out after removal of residual solids by filtration;

(iii) column chromatography (by the flash procedure) and medium pressure liquid chromatography (MPLC) were performed on Merck Kieselgel silica (Art. 9385) or Merck Lichroprep RP-18 (Art. 9303) reversed-phase silica obtained from E. Merck, Darmstadt, Germany or high pressure liquid chromatography (HPLC) was performed on C18 reverse phase silica, for example on a Dynamax C-18 60Å preparative reversed-phase column;

(iv) yields are given for illustration only and are not necessarily the maximum attainable;

(v) in general, the end-products of the Formula I have satisfactory microanalyses and their structures were confirmed by nuclear magnetic resonance (NMR) and/or mass spectral techniques; fast-atom bombardment (FAB) mass spectral data were obtained using a Platform spectrometer and, where appropriate, either positive ion data or negative ion data were collected; NMR chemical shift values were measured on the delta scale [proton magnetic resonance spectra were determined using a Varian Gemini 2000 spectrometer operating at a field strength of 300MHz or a Bruker AM250 spectrometer operating at a field strength of 250MHz]; the following abbreviations have been used: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad;

(vi) intermediates were not generally fully characterised and purity was assessed by thin layer chromatographic, HPLC, infra-red (IR) and/or NMR analysis;

(vii) melting points are uncorrected and were determined using a Mettler SP62 automatic melting point apparatus or an oil-bath apparatus; melting points for the end-products of the Formula I were determined after crystallisation from a conventional

organic solvent such as ethanol, methanol, acetone, ether or hexane, alone or in admixture; and

(viii) the following abbreviations have been used:-

DMF	N,N-dimethylformamide
DMSO	dimethylsulfoxide
MPLC	medium pressure liquid chromatography
HPLC	high pressure liquid chromatography

Example 1

N-[5-(2-Bicyclo[2.2.1]hept-2-ylacetylamino)-2-methylphenyl]-4-hydroxybenzamide

A solution of N-(5-amino-2-methylphenyl)-4-hydroxybenzamide (133 mg) in dry DMF (0.5 ml) was added to 2-norbornanylacetic acid (77 mg) followed by a solution of 1-(3-dimethylaminopropyl)-3-ethylcarbodimide hydrochloride (96 mg) in dry methylene chloride (3.0 ml). The reaction was stirred at ambient temperature for 5 hours. The solvents were removed by evaporation and the residue taken up into ethyl acetate (4.0 ml) and washed with water (3.0 ml). The aqueous layer was back extracted with ethyl acetate (4.0 ml) and the combined ethyl acetate extracts were evaporated to give 95 mg (53%) of the title product, shown to be 96% pure by HPLC.

The starting material was prepared as follows:

A) Oxalyl chloride (0.5 ml) was added slowly to a stirred suspension of 4-acetoxybenzoic acid (1.09 g), dry methylene chloride (30 ml) and DMF (one drop). The mixture was stirred for two hours at ambient temperature. A solution of 2-methyl-5-nitroaniline (760 mg) and pyridine (2.0 ml) in dry methylene chloride was added over 15 minutes. The reaction mixture was stirred for a further 2 hours, washed with 5% aqueous acetic acid (2 x 25 ml), water (20 ml) and 5% aqueous sodium hydrogen carbonate solution. The organic extract was dried over magnesium sulphate, filtered and evaporated to dryness. The residue was crystallised from ethyl acetate (100 ml) to give 800 mg (53%) of 4-acetoxy-N-(2-methyl-5-nitrophenyl)benzamide, melting point 207-208°C;

NMR Spectrum: ($DMSOd_6$) 2.3 (s, 3H), 7.31 (d, 2H), 7.56 (d, 1H), 8.02 (m, 3H), 8.47 (d, 1H), 10.12 (s, 1H); Mass Spectrum: $M+H^+$ 315;

Microanalysis: % Theory C 61.1, H 4.49, N 8.91

% Found C 61.0, H 4.3, N 8.8%.

B) A stirred mixture of 4-acetoxy-N-(2-methyl-5-nitrophenyl)benzamide (500 mg), ammonium formate (1.0 g) and 10% palladium on carbon (25 mg) in methanol (10 ml) was heated at 60°C for 2 hours. The reaction mixture was cooled and filtered through diatomaceous earth (Celite®). The filtrate was evaporated to dryness and the residue triturated with water. The crude product was filtered from the aqueous solution and crystallised from methanol to give 140 mg (31% yield) of N-(5-amino-2-methylphenyl)-4-hydroxybenzamide, Melting point 277-278°C;

NMR Spectrum: ($DMSOd_6$) 2.03 (s, 3H), 4.85 (s, 2H), 6.39 (m, 1H), 6.61 (d, 1H), 6.85 (m, 3H), 7.82 (d, 2H), 9.3 (s, 1H), 9.96 (s, 1H); Mass Spectrum: $M+H^+$ 243; Microanalysis: $C_{14}H_{14}N_2O_2$ requires C 69.4, H 5.8, N 11.6%; found C 69.1, H 5.8, N 11.5%.

Example 2

N-{5-[2-(3,4-Dichlorophenyl)acetylamino]-2-methylphenyl}-4-hydroxybenzamide

The method of Example 1 was repeated using 3,4-dichlorophenylacetic acid (0.5 mmol). The reaction mixture was evaporated and the residue taken up in ethyl acetate (4 ml), washed with 1M hydrochloric acid (3.0 ml) and water (3.0 ml). The ethyl acetate extract was evaporated to give the desired product, 132mg (68%), shown to be 92% pure by HPLC.

Example 3

N-[5-(3-Dimethylaminobenzamido)-2-methylphenyl]-4-hydroxybenzamide

N-(5-Amino-2-methylphenyl)-4-hydroxybenzamide (85 mg) was added to a stirred solution of 3-dimethylaminobenzoic acid (89 mg) in dry DMF (0.5 ml) followed by a solution of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (103 mg) in dry methylene chloride (3 ml) and 4-dimethylaminopyridine (131 mg; 1.07 mmol). The reaction was stirred at ambient temperature under argon for 18 hours. The reaction mixture was purified by MPLC on silica eluting in turn with 50%, 60% and 70% ethyl acetate in isohexane to give 17 mg (11%) of the title product; NMR Spectrum: ($DMSOd_6$) 2.17 (s, 3H), 2.96 (s, 6H), 6.80-6.95 (m, 3H), 7.15-7.35 (m, 4H), 7.58 (m, 1H), 7.79 (d, 1H), 7.87 (d, 2H), 9.62 (s, 1H), 9.95 (s, 1H), 10.10 (s, 1H); Mass Spectrum: $M+H^+$ 390;
Microanalysis: % Theory C 68.6, H 5.8, N 10.3 (0.2 CH_2Cl_2),
% Found C 68.1, H 5.7, N 10.9.

Example 4

N-[5-(4-Cyanobenzamido)-2-methylphenyl]-4-hydroxybenzamide

A solution of N-(5-amino-2-methylphenyl)-4-hydroxybenzamide (121 mg) in dry DMF (1.0 ml) was added to 4-cyanobenzoic acid (88 mg), and stirred. A solution of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (115 mg) in methylene

chloride (3.0 ml) was added and the mixture stirred at ambient temperature overnight. The solvent was then evaporated and the residue treated with 5% aqueous sodium hydrogen carbonate solution (3 ml) and extracted with ethyl acetate (3 x 5 ml). The organic layer was washed with water (3 ml) and filtered through a silica column eluting with ethyl acetate (3 x 15 ml). The solvent was evaporated and the residue crystallised from ethanol/water (1:1) to give the title product (70 mg), m.p. 297-299°C;

NMR Spectrum: ($DMSOd_6$) 2.2 (s, 3H), 6.88 (d, 2H), 7.23 (d, 1H), 7.56 (m, 1H), 7.85 (m, 3H), 8.0 (d, 2H), 8.12 (d, 2H), 9.62 (s, 1H), 10.02 (s, 1H), 10.45 (s, 1H); Mass Spectrum: $M+H^+$ 372;

Microanalysis : % Theory C 70.5, H 4.6, N 11.2,
% Found C 70.5, H 4.4, N 10.8.

Example 5

N-[5-(4-chlorobenzamido)-2-methylphenyl]-3,4-dimethoxybenzamide

Triethylamine (0.12 ml) was added to a stirred mixture of N-(5-amino-2-methylphenyl)-3,4-dimethoxybenzamide (0.1 g), 4-chlorobenzoyl chloride (0.067 ml), 4-dimethylaminopyridine (0.004 g) and methylene chloride (3 ml) and the mixture was stirred at ambient temperature for 16 hours. The reaction mixture was partitioned between methylene chloride and 2N hydrochloric acid. The organic phase was washed with a saturated aqueous solution of sodium bicarbonate and with brine, dried ($MgSO_4$) and evaporated. There was thus obtained the title compound as a solid (0.086 g);

NMR Spectrum: ($CDCl_3$) 2.26 (s, 3H), 3.94 (s, 6H), 6.91 (d, 1H), 7.18 (d, 1H), 7.29-7.81 (m, 8H), 8.09 (m, 2H); Mass Spectrum: $M+H^+$ 425.

The N-[5-amino-2-methylphenyl]-3,4-dimethoxybenzamide used as starting material was prepared as follows :-

A solution of 3,4-dimethoxybenzoyl chloride (11.5 g) in methylene chloride (100 ml) was added dropwise to a stirred mixture of 2-methyl-5-nitroaniline (8.74 g), pyridine (18.6 ml) and methylene chloride (200 ml) and the mixture was stirred at ambient temperature for 18 hours. The mixture was washed with 2N hydrochloric acid and with water, dried ($MgSO_4$) and evaporated. The resultant solid was dried under vacuum at 60°C. There was thus obtained N-(2-methyl-5-nitrophenyl)-3,4-dimethoxybenzamide (15.9 g), m.p. >300°C;

NMR Spectrum: ($CDCl_3$) 2.43 (s, 3H), 3.94 (m, 6H), 6.93 (m, 1H), 7.38 (m, 2H), 7.51 (m, 1H), 7.75 (br s, 1H), 7.94 (d, 1H), 8.89 (br m, 1H).

10% Palladium-on-carbon (4 g) was added to a stirred suspension of the material so obtained in methanol (1500 ml) and the mixture was stirred under an atmosphere of hydrogen gas. After cessation of hydrogen uptake, the catalyst was removed by filtration and the filtrate was evaporated. The residue was washed with diethyl ether and dried under vacuum at 60°C. There was thus obtained the required starting material (11.3 g), m.p. 157-158°C;

NMR Spectrum: ($CDCl_3$) 2.24 (s, 3H), 3.64 (br s, 2H), 3.95 (m, 6H), 6.44 (m, 1H), 6.93 (d, 1H), 6.98 (d, 1H), 7.38 (m, 1H), 7.54 (m, 2H), 7.6 (br s, 1H).

Example 6

N-[5-(3-bromobenzamido)-2-methylphenyl]-3,4-dimethoxybenzamide

3-Bromobenzoyl chloride (1.53 g) was added to a stirred mixture of N-(5-amino-2-methylphenyl)-3,4-dimethoxybenzamide (2 g), pyridine (1.7 ml) and methylene chloride (40 ml) and the mixture was stirred at ambient temperature for 18 hours. The precipitated solid was isolated, washed with diethyl ether and dried under vacuum at 60°C. There was thus obtained the title compound (1.89 g);m.p. 136-138°C;

NMR Spectrum: ($DMSOd_6$) 2.18 (s, 3H), 3.81 (s, 6H), 7.05 (d, 1H), 7.23 (d, 1H), 7.45 (t, 1H), 7.56 (m, 2H), 7.63 (m, 1H), 7.78 (m, 2H), 7.95 (d, 1H), 8.13 (d, 1H), 9.75 (br s, 1H), 10.31 (br s, 1H); Mass Spectrum: $M+H^+$ 469;

Elemental Analysis: Found: C, 59.1; H, 4.4; N, 5.9;

$C_{23}H_{21}N_2O_4Br$ requires C, 58.9; H, 4.5; N, 6.0%.

Example 7

N-[5-benzamido-2-methylphenyl]-3,4-dimethoxybenzamide

3,4-Dimethoxybenzoyl chloride (0.3 g) was added to a stirred mixture of N-(3-amino-4-methylphenyl)benzamide (0.23 g), triethylamine (0.4 ml) and methylene chloride (10 ml) and the mixture was stirred at ambient temperature for 16 hours. The precipitate was isolated, washed with water and with diethyl ether, dried under vacuum at 40°C. There was thus obtained the title compound (0.319 g);

NMR Spectrum: ($DMSOd_6$) 2.18 (s, 3H), 3.82 (s, 6H), 7.06 (d, 1H), 7.25 (d, 1H), 7.55

(m, 6H), 7.82 (s, 1H), 7.94 (d, 2H), 9.76(s, 1H), 10.20 (s, 1H); Mass Spectrum: $M+H^+$ 391.

The N-(3-amino-4-methylphenyl)benzamide used as a starting material was prepared as follows :-

Benzoyl chloride (1.9 ml) was added to a stirred mixture of 2, 4-diaminotoluene (2 g), triethylamine (5.57 ml) and methylene chloride (80 ml) and the mixture was stirred at ambient temperature for 16 hours. The mixture was washed with a saturated aqueous solution of sodium bicarbonate. The organic phase was dried ($MgSO_4$) and evaporated. The residue was triturated with a mixture of ethyl acetate and diethyl ether. There was thus obtained the required starting material (1.32 g); NMR Spectrum: ($DMSOd_6$) 2.01 (s, 3H), 4.8 (s, 2H), 6.82 (m 2H), 7.11 (s, 1H), 7.5 (m, 3H), 7.91 (m, 2H), 9.86 (s, 1H); Mass Spectrum: $M+H^+$ 227.

Example 8

N-[5-(3,4-dimethoxybenzamido)-2-methylphenyl]-3-dimethylaminobenzamide

Oxalyl chloride (1.14 g) was added to a stirred mixture of 3-dimethylaminobenzoic acid (1.23 g), DMF (1 drop) and methylene chloride (40 ml) and the mixture was stirred at ambient temperature for 3 hours. The solvent was evaporated and the residue was dissolved in methylene chloride (40 ml). The resultant solution was added dropwise to a stirred mixture of N-(3-amino-4-methylphenyl)-3,4-dimethoxybenzamide (1.78 g), pyridine (3.77 ml) and methylene chloride (20 ml) and the mixture was stirred at ambient temperature for 48 hours. The reaction mixture was washed in turn with water, a saturated aqueous sodium bicarbonate solution, brine and water. The organic solution was dried ($MgSO_4$) and evaporated. The solid so obtained was recrystallised from ethyl acetate and dried under vacuum at 60°C. There was thus obtained the title compound (0.359 g), m.p. 204-205°C; NMR Spectrum: ($DMSOd_6$) 2.28 (s, 3H), 3.01 (s, 6H), 3.93 (d, 6H), 6.88 (m, 2H), 7.09 (d, 1H), 7.18 (d, 1H), 7.26 (s, 1H), 7.33 (t, 1H), 7.41 (m, 1H); 7.5 (d, H), 7.76 (m, 2H), 8.05 (br s, 1H), 8.13 (d, 1H); Mass Spectrum: $M+H^+$ 434.

The N-(3-amino-4-methylphenyl)-3,4-dimethoxybenzamide used as starting material was prepared as follows :-

A solution of 3,4-dimethoxybenzoyl chloride (13.2 g) in methylene chloride (200 ml) was added dropwise to a stirred mixture of 4-methyl-3-nitroaniline (10 g), pyridine (21.3 ml),

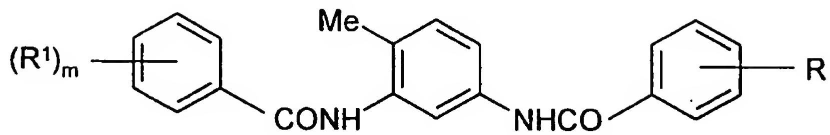
4-dimethylaminopyridine (0.4 g) and methylene chloride (100 ml) and the resultant solution was stirred at ambient temperature for 18 hours. The reaction mixture was washed with 2N hydrochloric acid and water, dried ($MgSO_4$) and evaporated. The residue was triturated under diethyl ether and the resultant solid was dried under vacuum at 60°C. There was thus obtained N-(4-methyl-3-nitrophenyl)-3,4-dimethoxybenzamide (18.1 g), m.p. 148-149°C; NMR Spectrum: ($CDCl_3$) 2.58 (s, 3H), 3.96 (s, 6H), 6.92 (d, 1H), 7.33 (d, 1H), 7.43 (m, 1H), 7.51 (d, 1H), 7.9 (m, 1H), 7.97 (br s, 1H), 8.24 (d, 1H).

Ammonium formate (33.9 g) was added to a stirred suspension of N-(4-methyl-3-nitrophenyl)-3,4-dimethoxybenzamide (17 g) and 10% palladium-on-carbon (4 g) in ethanol (650 ml) and the mixture was stirred and heated to reflux for 1.5 hours. The reaction mixture was allowed to cool to ambient temperature and filtered. The filtrate was evaporated and the residue was partitioned between methylene chloride and a saturated aqueous sodium bicarbonate solution. The organic phase was washed with water, dried ($MgSO_4$) and evaporated. The residue was triturated under diethyl ether and the resultant solid was dried under vacuum at 60°C. There was thus obtained the required starting material (12.6 g), m.p. 143-144°C; NMR Spectrum: ($CDCl_3$) 2.13 (s, 3H), 3.65 (br s, 2H), 3.93 (s, 6H), 6.73 (m, 1H), 6.93 (d, 1H), 6.87 (m, 1H), 7.0 (m, 1H), 7.28 (d, 1H), 7.36 (m, 1H), 7.48 (d, 1H), 7.7 (br s, 1H).

Example 9

Using an analogous procedure to that described in Example 3, 5, 6 or 7, the appropriate benzoyl chloride was reacted with the appropriate aniline to give the compounds described in Table I. With reference to the chemical formula immediately hereinafter in Table I and when an analogous procedure to that described in Example 3, 5 or 6 is employed, the appropriate benzoyl chloride is of the formula $R\text{-}C_6H_4\text{-}COCl$ and when an analogous procedure to that described in Example 7 is employed, the appropriate benzoyl chloride is of the formula $(R^1)_m\text{-}C_6H_{(5\text{-}m)}\text{-}COCl$

Table I



No.	$(R^1)_m$	R	Method	Note
1	3,4-dimethoxy	4-bromo	Ex. 6	a
2	3,4-dimethoxy	4-fluoro	Ex. 6	b
3	3,4-dimethoxy	3-benzyloxy	Ex. 6	c
4	3,4-dimethoxy	4-benzyloxy	Ex. 6	d
5	3,4-dimethoxy	3-nitro	Ex. 6	e
6	3,4-dimethoxy	4-cyano	Ex. 5	f
7	3,4-dimethoxy	3-dimethylamino	Ex. 7	g
8	3,4-dimethoxy	4-morpholino	Ex. 6	h
9	3,4-dimethoxy	4-(4-thiamorpholino)	Ex. 6	i
10	3,4-dimethoxy	3,4-dimethoxy	Ex. 5	j
11	4-hydroxy	hydrogen	Ex. 3	k
12	4-hydroxy	2-fluoro-6-chloro	Ex. 3	l
13	4-hydroxy	4-benzyloxy	Ex. 3	m
14	4-hydroxy	3,5-dimethoxy	Ex. 3	n
15	4-hydroxy	4-phenyl	Ex. 3	o
16	4-hydroxy	4-nitro	Ex. 3	p
17	4-acetoxy	4-cyano	Ex. 7	q
18	4-propyl	3-dimethylamino	Ex. 7	r
19	4-ethyl	3-dimethylamino	Ex. 7	s
20	4-tert-butyl	3-dimethylamino	Ex. 7	t
21	4-butyl	3-dimethylamino	Ex. 7	u
22	3,4-dimethyl	3-dimethylamino	Ex. 7	v
23	2-methoxy	3-dimethylamino	Ex. 7	w

No.	$(R^1)_m$	R	Method	Note
24	3-methoxy	3-dimethylamino	Ex. 7	x
25	4-methoxy	3-dimethylamino	Ex. 7	y
26	3-ethoxy	3-dimethylamino	Ex. 7	z
27	4-ethoxy	3-dimethylamino	Ex. 7	aa
28	4-isopropoxy	3-dimethylamino	Ex. 7	bb
29	3-butoxy	3-dimethylamino	Ex. 7	cc
30	2,4-dimethoxy	3-dimethylamino	Ex. 7	dd
31	3,4-diethoxy	3-dimethylamino	Ex. 7	ee
32	3,4,5-trimethoxy	3-dimethylamino	Ex. 7	ff
33	3-chloro	3-dimethylamino	Ex. 7	gg
34	4-chloro	3-dimethylamino	Ex. 7	hh
35	2-fluoro	3-dimethylamino	Ex. 7	ii
36	3,5-difluoro	3-dimethylamino	Ex. 7	jj
37	3-trifluoromethyl	3-dimethylamino	Ex. 7	kk
38	4-trifluoromethyl	3-dimethylamino	Ex. 7	ll
39	3-cyano	3-dimethylamino	Ex. 7	mm
40	4-cyano	3-dimethylamino	Ex. 7	nn
41	4-methoxycarbonyl	3-dimethylamino	Ex. 7	oo
42	4-cyano	4-cyano	Ex. 5	pp
43	hydrogen	hydrogen	Ex. 7	qq
44	3,4,5-trimethoxy	4-cyano	Ex. 7	rr
45	3,4,5-trimethoxy	hydrogen	Ex. 7	ss
46	3,4,5-trimethoxy	3-trifluoromethyl	Ex. 7	tt
47	3,4,5-trimethoxy	3-morpholino	Ex. 6	uu
48	3-bromo	3-dimethylamino	Ex. 6	vv
49	3-nitro	3-dimethylamino	Ex. 6	ww
50	3-morpholino	3-morpholino	Ex. 6	xx
51	3-(4-methylpiperazin-1-yl)methyl	hydrogen	Ex. 5	yy
52	3-(4-methylpiperazin-1-yl)methyl	3-trifluoromethyl	Ex. 5	zz

No.	$(R^1)_m$	R	Method	Note
53	3-(4-methylpiperazin-1-yl)methyl	2-fluoro	Ex. 5	aaa
54	3-(4-methylpiperazin-1-yl)methyl	4-fluoro	Ex. 5	bbb
55	3-(4-methylpiperazin-1-yl)methyl	2-chloro	Ex. 5	ccc
56	3-(4-methylpiperazin-1-yl)methyl	3-chloro	Ex. 5	ddd
57	3-(4-methylpiperazin-1-yl)methyl	4-chloro	Ex. 6	eee
58	3-(4-methylpiperazin-1-yl)methyl	2,5-difluoro	Ex. 6	fff
59	3-(4-methylpiperazin-1-yl)methyl	3,5-difluoro	Ex. 5	ggg
60	3-(4-methylpiperazin-1-yl)methyl	2,4-dichloro	Ex. 5	hhh
61	3-(4-methylpiperazin-1-yl)methyl	3,4-dichloro	Ex. 5	iii
62	3-(4-methylpiperazin-1-yl)methyl	2-methoxy	Ex. 6	jjj
63	3-(4-methylpiperazin-1-yl)methyl	4-methoxy	Ex. 5	kkk
64	3-(4-methylpiperazin-1-yl)methyl	3-ethoxy	Ex. 5	lll
65	3-(4-methylpiperazin-1-yl)methyl	3,4-dimethoxy	Ex. 5	mmm
66	3-(4-methylpiperazin-1-yl)methyl	3-cyano	Ex. 5	nnn
67	3-(4-methylpiperazin-1-yl)methyl	4-methoxycarbonyl	Ex. 5	ooo
68	3-(4-methylpiperazin-1-yl)methyl	3-morpholino	Ex. 5	ppp

Notes

a) The reactants were 4-bromobenzoyl chloride and N-(5-amino-2-methylphenyl)-3,4-dimethoxybenzamide. The product gave the following data : m.p. 221-222°C; NMR ($DMSOd_6$) 2.18 (s, 3H), 3.83 (s, 6H), 7.06 (d, 1H), 7.23 (d, 1H), 7.54 (m, 2H), 7.63 (m, 1H), 7.72 (d, 2H), 7.8 (d, 1H), 7.9 (d, 2H), 9.75 (s, 1H), 10.28 (br s, 1H); Mass M+H 469.

b) The product gave the following data : m.p. 210-211°C; NMR ($DMSOd_6$) 2.18 (s, 3H), 3.83 (s, 6H), 7.07 (d, 1H), 7.23 (d, 1H), 7.35 (t, 2H), 7.55 (m, 2H), 7.57 (d, 1H), 7.63 (m, 1H), 7.8 (d, 1H), 8.03 (m, 2H), 9.75 (br s, 1H),10.39 (br s, 1H); Mass M+H 409.

c) The product gave the following data : m.p. 208-209°C; NMR ($DMSOd_6$) 2.21 (s, 3H), 3.83 (s, 6H), 5.18 (s, 2H), 7.06 (d, 1H), 7.21 (m, 2H), 7.4 (m, 5H), 7.55 (m, 3H), 7.62 (m, 1H), 7.8 (d, 1H), 9.77 (br s, 1H), 10.17 (br s, 1H); Mass M+H 497.

d) The product gave the following data : m.p. 186-187°C; NMR ($DMSOd_6$) 2.17 (s, 3H), 3.83 (s, 6H), 5.18 (s, 2H), 7.07 (d, 1H), 7.13 (d, 2H), 7.2 (d, 1H), 7.37 (m, 3H), 7.45 (m, 2H), 7.55 (m, 2H), 7.63 (m, 1H) , 7.8 (d, 1H), 7.94 (d, 2H), 9.74 (br s, 1H), 10.04 (br s, 1H); Mass M+H 497.

e) The product gave the following data : m.p. 232-233°C; NMR ($DMSOd_6$) 2.19 (s, 3H), 3.83 (s, 6H), 7.07 (d, 1H), 7.24 (d, 1H), 7.61 (m, 3H), 7.83 (t, 2H), 8.45 (m, 2H), 8.79 (d, 1H), 9.76 (s, 1H), 10.55 (br s, 1H); Mass M-H 434.

f) The reactants were 4-cyanobenzoyl chloride and N-(5-amino-2-methylphenyl)-3,4-dimethoxybenzamide. The product gave the following data : NMR ($CDCl_3$) 2.23 (s, 3H), 3.95 (m, 6H), 6.69-8.45 (m, 12H); Mass M+H 416.

g) The reactants were 3,4-dimethoxybenzoyl chloride and N-(3-amino-4-methylphenyl)-3-dimethylaminobenzamide. The product gave the following data : NMR ($DMSOd_6$) 2.18 (s, 3H), 2.94 (s, 6H), 3.82 (s, 6H), 6.88 (d, 1H), 7.05 (d, 1H), 7.20 (m, 3H), 7.28 (m, 1H), 7.58 (m, 2H), 7.63 (d, 1H), 7.78 (s, 1H), 9.76 (s, 1H), 10.08 (s, 1H); Mass M+H 434.

The N-(3-amino-4-methylphenyl)-3-dimethylaminobenzamide used as starting material was prepared as follows :

Oxalyl chloride (13.0 ml) was added dropwise to a stirred mixture of 3-dimethylaminobenzoic acid (20.3 g) and DMF (a few drops) which had been cooled to 0°C. The mixture was allowed to warm to ambient temperature and was stirred for 4 hours. The resultant mixture was evaporated and the residue was dissolved in methylene chloride (150 ml). 4-Methyl-3-nitroaniline (15.2 g) and triethylamine (27.9 ml) were added in turn and the resultant mixture was stirred at ambient temperature for 16 hours. The reaction mixture was washed in turn with water, with a saturated solution of sodium bicarbonate and with brine, dried ($MgSO_4$) and evaporated. The residue was triturated under a mixture of ethyl acetate and isohexane. The solid so obtained was filtered off and recrystallised from ethanol to give N-(3-nitro-4-methylphenyl)-3-dimethylaminobenzamide (6.1 g); NMR ($DMSOd_6$) 2.46 (s, 3H), 2.95 (s, 6H), 6.92 (d, 1H), 7.22 (m, 2H), 7.32 (t, 1H), 7.45 (d, 1H), 7.97 (d, 1H), 8.53 (s, 1H), 10.43 (s, 1H); Mass $M+H^+$ 300;

After repetition of the previous reactions, a sample (8.25 g) was added to a

stirred suspension of ammonium formate (17.4 g), and 10% palladium-on-carbon (1 g) in methanol (250 ml). The mixture was stirred and heated to reflux for 4 hours. The mixture was allowed to cool and then filtered. The filtrate was evaporated and water was added to the residue. The resultant solid was isolated and washed in turn with water, with ethyl acetate and with diethyl ether. The solid was dried in a vacuum oven at 40°C to give N-(3-amino-4-methylphenyl)-3-dimethylaminobenzamide (6.89 g); NMR ($DMSOd_6$) 2.0 (s, 3H), 2.94 (s, 6H), 4.78 (s, 2H), 6.82 (m, 3H), 7.07 (s, 1H), 7.17 (m, 2H), 7.25 (m, 1H), 9.74 (s, 1H); Mass $M+H^+$ 270.

h) The reactants were 4-morpholinobenzoyl chloride and N-(5-amino-2-methylphenyl)-3,4-dimethoxybenzamide. The product gave the following data : m.p. 226-228°C; NMR ($DMSOd_6$) 2.18 (s, 3H), 3.23 (t, 4H), 3.76 (t, 4H), 3.82 (s, 6H), 7.01 (d, 2H), 7.08 (d, 1H), 7.19 (d, 1H), 7.56 (m, 2H), 7.62 (d, 1H), 7.79 (s, 1H), 7.88 (d, 2H), 9.75 (s, 1H), 9.95 (s, 1H); Mass M+H 476.

The 4-morpholinobenzoyl chloride used as a starting material was prepared as follows :-

Morpholine (2.16 g) was added to a stirred mixture of benzyl 4-fluorobenzoate (3.1 g), potassium carbonate (4.48 g) and DMSO (45 ml) and the reaction mixture was heated to 100°C for 36 hours. The mixture was cooled to ambient temperature and partitioned between diethyl ether and water. The organic phase was washed with brine, dried ($MgSO_4$) and evaporated. The residue was recrystallised from a 3:1 mixture of hexane and ethyl acetate to give benzyl 4-morpholinobenzoate (2.24 g) as a colourless solid, m.p. 85-86°C; NMR Spectrum: ($CDCl_3$) 3.19 (t, 4H), 3.77 (t, 4H), 5.23 (s, 2H), 6.78 (d, 2H), 7.30 (m, 5H), 7.9 (d, 2H).

Palladium-on-carbon catalyst (0.12 g) was added to a stirred solution of the above benzyl ester (1.50 g) in a mixture of ethanol (100 ml) and ethyl acetate (15 ml). The mixture was stirred under an atmosphere of hydrogen. After cessation of hydrogen uptake, the catalyst was removed by filtration and the filter cake was washed with ethanol. The combined filtrates were evaporated to give 4-morpholinobenzoic acid (0.69 g); NMR Spectrum: ($DMSOd_6$) 3.22 (t, 4H), 3.72 (t, 4H), 6.96 (d, 2H), 7.78 (d, 2H).

Oxalyl chloride (0.062 ml) was added dropwise to a stirred suspension of

4-morpholinobenzoic acid (0.113 g) in methylene chloride (5 ml) which had been cooled to 0°C. DMF (1 drop) was added and the mixture was stirred at ambient temperature for 4 hours. The solvent was evaporated to give 4-morpholinobenzoyl chloride which was used without further purification.

i) The product gave the following data : m.p. 236-238°C; NMR ($DMSOd_6$) 2.18 (s, 3H), 2.61 (t, 4H), 3.72 (t, 4H), 3.82 (s, 6H), 6.95 (d,2H), 7.06 (d, 1H), 7.18 (d, 1H), 7.56 (m, 2H), 7.62 (d, 1H), 7.8 (s, 1H), 7.82 (d, 2H), 9.75 (s, 1H), 9.9 (s, 1H); Mass M+H 492.

The 4-(4-thiamorpholino)benzoyl chloride used as a starting material was prepared as follows :-

Ethyl 4-(4-thiamorpholino)benzoate was prepared from ethyl 4-fluorobenzoate and thiamorpholine using an analogous procedure to that described in Note h) for the preparation of benzyl 4-morpholinobenzoate. The material so obtained had m.p. 46.5-47.5°C and NMR ($CDCl_3$) 1.3 (t, 3H), 2.62 (t, 4H), 3.63 (t, 4H), 4.23 (m, 2H), 6.78 (d, 2H), 7.82 (d, 2H).

Ethyl 4-(4-thiamorpholino)benzoate (1.02 g) was added to a solution of sodium hydroxide (0.32 g) in 90% ethanol (10 ml) and the solution was stirred at ambient temperature for 18 hours. The ethanol was evaporated and 1N hydrochloric acid (8 ml) was added to the residue. The mixture was stirred for 1 hour. The precipitate was isolated and washed with water. The material was triturated under ethyl acetate to give 4-(4-thiamorpholino)benzoic acid (0.66 g) as a colourless solid, m.p. 238-240°C; NMR ($DMSOd_6$) 2.6 (t, 4H), 3.73 (t, 4H), 6.91 (d, 2H), 7.75 (d, 2H), 12.2 (s, 1H).

The acid so obtained was converted into the required benzoyl chloride using an analogous procedure to that described in Note h).

j) The reactants were 3,4-dimethoxybenzoyl chloride and 2,4-diaminotoluene. The product gave the following data : NMR ($DMSOd_6$) 2.18 (s, 3H), 3.82 (s, 12H), 7.06 (d, 2H), 7.21 (d, 1H), 7.57 (m, 5H), 7.76 (s, 1H), 9.74 (s, 1H), 10.01 (s, 1H); Mass M+H 451.

k) The reactants were benzoyl chloride and N-(5-amino-2-methylphenyl)-4-hydroxybenzamide. The product gave the following data : NMR ($DMSOd_6$) 2.2 (s, 3H), 6.87 (d, 2H), 7.21 (d, 1H), 7.56 (m, 4H), 7.9 (m, 5H), 9.6 (s, 1H), 10.0 (s, 1H),

10.2 (s, 1H); Mass M+H 347.

l) The product gave the following data : Mass M+H 399.

m) The product gave the following data : NMR ($DMSOd_6$) 2.19 (s, 3H), 5.2 (s, 2H), 6.68 (d, 2H), 7.15 (m, 3H), 7.4 (m, 5H), 7.58 (m, 1H), 7.8 (d, 1H), 7.88 (d, 2H), 7.95 (d, 2H), 9.6 (s, 1H), 10.02 (s, 1H), 10.05 (s, 1H); Mass M+H 453.

n) The product gave the following data : Mass M+H 407.

o) The product gave the following data : NMR ($DMSOd_6$) 2.21 (s, 3H), 6.87 (d, 2H), 7.22 (d, 1H), 7.48 (m, 4H), 7.61 (m, 1H), 7.8 (m, 6H), 8.08 (d, 2H), 9.63 (s, 1H), 10.05 (s, 1H) 10.25 (s, 1H); Mass M+H 423.

p) The product gave the following data : NMR ($DMSOd_6$) 2.18 (s, 3H), 3.68 (s, 2H), 6.86 (d, 2H), 7.17 (d, 1H), 7.35 (m, 2H), 7.6 (m, 3H), 7.86 (d, 2H), 9.54 (s, 1H), 9.99 (s, 1H), 10.12 (s, 1H); Mass M+H 406.

q) The reactants were 4-acetoxybenzoyl chloride and N-(3-amino-4-methylphenyl)-4-cyanobenzamide. 4-Dimethylaminopyridine (0.15 equivalents) was added to catalyse the reaction. The product gave the following data : NMR ($DMSOd_6$) 2.18 (s, 3H), 2.26 (s, 3H), 7.25 (m, 3H), 7.57 (d, 1H), 7.84 (s, 1H), 8.0 (m, 4H), 8.11 (d, 2H), 9.91 (s, 1H), 10.46 (s, 1H); Mass: (M-H) 412.

The N-(3-amino-4-methylphenyl)-4-cyanobenzamide used as starting material was prepared as follows :

Triethylamine (23 ml) was added to a suspension of 3-nitro-4-methylaniline (0.8 g), 4-cyanobenzoyl chloride (13.1 g), 4-dimethylaminopyridine (0.8 g) in methylene chloride (200 ml) which had been cooled to 0°C. The reaction mixture was allowed to warm to ambient temperature and was stirred for 5 hours. The mixture was partitioned between methylene chloride 0.5N hydrochloric acid solution. The organic phase was dried ($MgSO_4$) and evaporated and the residue was triturated under isohexane. The solid was isolated and dried under vacuum at 55°C. There was thus obtained (3-nitro-4-methylphenyl)-4-cyanobenzamide (18.3 g); NMR ($DMSOd_6$) 2.5 (s, 3H), 7.49 (d, 1H), 7.96 (m, 1H), 8.05 (d, 2H), 8.12 (d, 2H), 8.51 (d, 1H), 10.77 (s, 1H).

A solution of tin(II) chloride dihydrate (15.4 g) in concentrated hydrochloric acid (80 ml) was added to a suspension of N-(3-nitro-4-methylphenyl)-

4-cyanobenzamide (6.39 g) in acetic acid (120 ml). The mixture was stirred and heated to reflux for 2 hours. The mixture was allowed to cool to ambient temperature and was basified by the addition of 2N sodium hydroxide solution. The precipitated solid was isolated and dried under vacuum at 55°C to give N-(3-amino-4-methylphenyl)-4-cyanobenzamide (5.62 g); NMR ($DMSOd_6$) 2.01 (s, 3H), 4.85 (s, 2H), 6.80 (d, 1H), 6.86 (d, 1H), 7.11 (s, 1H), 7.96 (d, 2H), 8.06 (d, 2H), 10.11 (s, 1H).

r) The reactants were 4-propylbenzoyl chloride and N-(3-amino-4-methylphenyl)-3-dimethylaminobenzamide. The product gave the following data : NMR ($DMSOd_6$) 0.89 (m, 3H), 1.61 (m, 2H), 2.19 (s, 3H), 2.62 (m, 2H), 2.95 (s, 6H), 6.89 (d, 1H), 7.22 (m, 3H), 7.30 (m, 3H), 7.57 (m, 1H), 7.78 (m, 1H), 7.9 (m, 2H), 9.8 (s, 1H), 10.08 (s, 1H); Mass M+H 416.

s) The product gave the following data : Mass M+H 402.

t) The product gave the following data : NMR ($DMSOd_6$) 2.18 (s, 3H), 2.94 (s, 6H), 6.9 (d, 1H), 7.20 (m, 3H), 7.28 (t, 1H), 7.55 (m, 3H), 7.8 (s, 1H), 7.91 (d, 2H), 9.79 (s, 1H), 10.08 (s, 1H); Mass M+H 430.

u) The product gave the following data : Mass M+H 430.

v) The product gave the following data : Mass M+H 402.

w) The product gave the following data : NMR ($DMSOd_6$) 2.28 (s, 3H), 2.95 (s, 6H), 3.99 (s, 3H), 6.9 (m, 1H), 7.11 (m, 1H), 7.25 (m, 5H), 7.55 (m, 2H), 7.9 (d, 1H), 8.33 (s, 1H), 9.81 (s, 1H), 10.09 (s, 1H); Mass M+H 404.

x) The product gave the following data : NMR ($DMSOd_6$) 2.29 (s, 3H), 3.0 (s, 6H), 3.87 (s, 3H), 6.86 (m, 1H), 7.1 (m, 2H), 7.2 (d, 1H), 7.28 (m, 2H), 7.4 (m, 2H), 7.45 (br s, 1H), 7.72 (m, 1H), 7.77 (br s, 1H), 7.98 (br s, 1H), 8.08 (d, 1H); Mass M+H 404.

y) The product gave the following data : NMR ($DMSOd_6$) 2.18 (s, 3H), 2.94 (s, 6H), 3.82 (s, 3H), 6.89 (d, 1H), 7.04 (d, 2H), 7.2 (m, 3H), 7.29 (td, 1H), 7.56 (d, 1H), 7.78 (s, 1H), 7.95 (d, 2H), 9.72 (s, 1H), 10.07 (s, 1H); Mass M+H 404.

z) The product gave the following data : Mass M+H 418.

aa) The product gave the following data : Mass M+H 418.

bb) The product gave the following data : NMR ($DMSOd_6$) 1.28 (d, 6H), 2.18 (s, 3H), 2.95 (s, 6H), 4.72 (m, 1H); 6.89 (d, 1H), 7.01 (d, 2H), 7.19 (m, 3H), 7.27 (m, 1H), 7.56

(d, 1H), 7.78 (s, 1H), 7.93 (d, 2H), 9.7 (s, 1H), 10.08 (s, 1H); Mass M+H 432.

cc) The product gave the following data : NMR ($DMSOd_6$) 0.93 (t, 3H), 1.44 (m, 2H), 2.71 (m, 2H), 2.18 (s, 3H), 2.94 (s, 6H), 4.04 (t, 2H), 6.9 (d, 1H), 7.03 (d, 2H), 7.26 (m, 4H), 7.56 (d, 1H), 7.8 (s, 1H), 7.94 (d, 2H), 9.71 (s, 1H), 10.08 (s, 1H); Mass M+H 446.

dd) The product gave the following data : NMR ($DMSOd_6$) 2.27 (s, 3H), 2.95 (s, 6H), 3.85 (s, 3H), 4.05 (s, 3H), 6.72 (m, 2H), 6.89 (d, 1H), 7.22 (m, 4H), 7.51 (d, 1H), 7.95 (d, 1H), 8.42 (d, 1H), 9.72 (s, 1H), 10.01 (s, 1H); Mass M+H 434.

ee) The product gave the following data : Mass M+H 462. The 3,4-diethoxybenzoyl chloride used as a starting material was prepared by the reaction of 3,4-diethoxybenzoic acid and oxalyl chloride.

ff) The product gave the following data : NMR ($DMSOd_6$) 2.18 (s, 3H), 2.94 (s, 6H), 3.72 (s, 3H), 3.84 (s, 6H), 6.89 (d, 1H), 7.25 (m, 6H), 7.56 (d, 1H), 7.77 (s, 1H), 9.86 (s, 1H), 10.09 (s, 1H); Mass M+H 464.

gg) The product gave the following data : Mass M+H 408.

hh) The product gave the following data : Mass M+H 408.

ii) The product gave the following data : NMR ($DMSOd_6$) 2.22 (s, 3H), 2.95 (s, 6H), 6.9 (d, 1H), 7.26 (m, 6H), 7.56 (m, 2H), 7.71 (t, 1H), 7.92 (s, 1H), 9.82 (s, 1H), 10.1 (s, 1H); Mass M+H 392.

jj) The product gave the following data : NMR ($DMSOd_6$) 2.18 (s, 3H), 2.95 (s, 6H), 6.89 (d.1H), 7.25 (m, 4H), 7.55 (m, 2H), 7.63 (m, 2H), 7.79 (s, 1H), 10.06 (s, 1H), 10.1 (s, 1H); Mass M+H 410.

kk) The product gave the following data : NMR ($DMSOd_6$) 2.19 (s, 3H) 2.95 (s, 6H) 6.9 (d, 1H), 7.24 (m, 4H), 7.58 (d, 1H) 7.78 (m, 2H), 7.96 (d, 1H), 8.28 (d, 2H) 10.11 (s, 1H), 10.19 (s, 1H); Mass M+H 442.

ll) The product gave the following data : Mass M+H 442.

mm) The product gave the following data : NMR ($DMSOd_6$) 2.19 (s, 3H), 2.95 (s, 6H), 6.89 (d, 1H), 7.24 (m, 4H), 7.58 (d, 1H), 7.75 (t, 1H), 7.81 (s, 1H), 8.06 (d, 1H), 8.23 (d, 1H), 8.4 (s, 1H), 10.11 (s, 2H); Mass M+H 399.

nn) The product gave the following data : Mass M+H 399.

oo) The product gave the following data : NMR ($DMSOd_6$) 2.19 (s, 3H), 2.95 (s, 6H), 3.89

(s, 3H), 6.89 (d, 1H), 7.25 (m, 4H), 7.57 (d, 1H), 7.8 (s, 1H), 8.08 (s, 4H), 9.8 (s, 1H), 10.1 (s, 1H); Mass M+H 432.

pp) The reactants were 4-cyanobenzoyl chloride and 2,4-diaminotoluene. The product gave the following data : NMR ($DMSOd_6$) 2.02 (s, 3H), 7.44 (d, 1H), 7.59 (d, 1H), 7.84 (d, 1H), 8.0 (m, 4H), 8.1 (m, 4H), 10.16 (s, 1H), 10.48 (s, 1H); Mass M+H 381.

qq) The reactants were benzoyl chloride and 2,4-diaminotoluene. The minor product was N-(5-benzamido-2-methylphenyl)benzamide which gave the following data : NMR ($DMSOd_6$) 2.2 (s, 3H), 7.21 (d, 1H), 7.5 (m, 7H), 7.84 (s, 1H), 7.98 (m, 4H), 9.81 (s, 1H), 10.23 (s, 1H); Mass M+H 331. The major product was N-(3-amino-4-methylphenyl)benzamide which gave the following data : NMR ($DMSOd_6$) 2.01 (s, 3H), 4.80 (s, 2H), 6.82 (m 2H), 7.11 (s, 1H), 7.5 (m, 3H), 7.91 (m, 2H), 9.86 (s, 1H); Mass M+H 227.

rr) The reactants were 3,4,5-trimethoxybenzoyl chloride and N-(3-amino-4-methylphenyl)-4-cyanobenzamide. 4-Dimethylaminopyridine (0.1 equivalents) was added to catalyse the reaction. On completion of the reaction, the reaction mixture was evaporated and the residue was triturated under 2N aqueous hydrochloric acid. The resultant solid was isolated, washed with a saturated aqueous sodium bicarbonate solution and with water and dried under vacuum at 55°C. The product gave the following data : NMR ($DMSOd_6$) 2.2 (s, 3H), 3.72 (s, 3H), 3.85 (s, 6H), 7.25 (d, 1H), 7.33 (s, 2H), 7.56 (d, 1H), 7.81 (s, 1H), 8.0 (d, 2H), 8.1 (d, 2H), 9.87 (s, 1H), 10.46 (s, 1H); Mass M-H 444.

ss) 4-Dimethylaminopyridine (0.1 equivalents) was added to catalyse the reaction and the work-up described in Note rr) was used. The product gave the following data : NMR ($DMSOd_6$) 2.19 (s, 3H), 3.73 (s, 3H), 3.85 (s, 6H), 7.24 (d, 1H), 7.32 (s, 2H), 7.55 (m, 4H), 7.82 (s, 1H), 7.94 (d, 2H), 9.86 (br s, 1H), 10.22 (br s, 1H); Mass M-H 419.

tt) 4-Dimethylaminopyridine (0.1 equivalents) was added to catalyse the reaction and the work-up described in Note rr) was used. The product gave the following data : NMR ($DMSOd_6$) 2.2 (s, 3H), 3.73 (s, 3H), 3.84 (s, 6H), 7.25 (d, 1H), 7.32 (s, 2H), 7.58 (d, 1H), 7.78 (m, 2H), 7.95 (d, 1H), 8.25 (m, 2H), 9.86 (s, 1H), 10.44 (s, 1H); Mass M-H 487.

uu) The reactants were 3-morpholinobenzoyl chloride and N-(5-amino-2-methylphenyl)-

3,4,5-trimethoxybenzamide. On completion of the reaction, the reaction mixture was evaporated and the residue was azeotroped with toluene. The resultant residue was stirred under methanol for 30 minutes. The solid so obtained was isolated and dried. The product gave the following data : NMR ($DMSOd_6$) 2.2 (s, 3H), 3.2 (t, 4H), 3.74 (m, 7H), 3.84 (s, 6H), 7.13 (m, 1H), 7.22 (d, 1H), 7.32 (s, 2H), 7.36 (d, 1H), 7.43 (s, 1H), 7.58 (d, 1H), 7.79 (s, 1H), 9.84 (s, 1H), 10.12 (s, 1H); Mass M+H 506.

The 3-morpholinobenzoyl chloride used as a starting material was prepared as follows:-

A mixture of ethyl 3-bromobenzoate (1.92 ml), morpholine (1.25 ml), 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (0.336 g), sodium tert-butoxide (1.615 g) and tris(dibenzylideneacetone)dipalladium(0) (0.33 g) and toluene (25 ml) was stirred and heated to 90°C for 18 hours under argon. The reaction mixture was allowed to cool to ambient temperature and extracted with 1N aqueous hydrochloric acid. The aqueous phase was basified with concentrated sodium hydroxide solution and extracted with ethyl acetate. The organic phase was dried ($MgSO_4$) and evaporated. The residual oil was purified by column chromatography on silica gel using a 47:3 mixture of methylene chloride and methanol as eluent. There was thus obtained N-(3-morpholinobenzoyl)morpholine (0.45 g).

A mixture of the material so obtained, 5M sodium hydroxide solution (2.5 ml) and butanol (2 ml) was stirred and heated to 115°C for 18 hours. The mixture was evaporated and the residue was acidified by the addition of 1N aqueous hydrochloric acid solution (12.5 ml). The resultant precipitate was isolated, washed with water and dried to give 3-morpholinobenzoic acid (0.15 g); NMR ($DMSOd_6$) 3.1 (t, 4H), 3.73 (t, 4H), 7.19 (d, 1H), 7.32 (d, 1H), 7.38 (t, 1H), 7.42 (s, 1H).

Oxalyl chloride (0.14 ml) was added to a solution of 3-morpholinobenzoic acid (0.28 g) in methylene chloride (10 ml) which contained DMF (2 drops). The reaction mixture was stirred for 18 hours at ambient temperature. The mixture was evaporated and azeotroped with toluene to give 3-morpholinobenzoyl chloride (0.3 g); Mass M+H 222.

vv) The product gave the following data : m.p. 235-236°C: NMR ($DMSOd_6$) 2.19 (s, 3H), 2.95 (s, 6H), 6.9 (m, 1H), 7.2 (m, 3H), 7.3 (t, 1H), 7.48 (t,1H), 7.56 (m, 1H), 7.78

(m, 2H), 7.97 (d, 1H), 8.14 (d, 1H), 10.02 (br s, 1H), 10.09 (br s, 1H); Mass M+H 453.

ww) The product gave the following data : m.p. 219-220°C: NMR ($DMSOd_6$) 2.2 (s, 3H), 2.95 (s, 6H), 6.92 (d, 1H), 7.23 (m, 3H), 7.28 (t, 1H), 7.575 (m, 1H), 7.83 (m, 2H), 8.43 (m, 2H), 8.8 (d, 1H), 10.12 (br s, 1H), 10.33 (br s, 1H); Mass M-H 417.

xx) On completion of the reaction, the reaction mixture was washed with water and with a saturated aqueous sodium bicarbonate solution. The mixture was evaporated and the residue was azeotroped with toluene. The resultant residue was purified by column chromatography using a 9:1 mixture of methylene chloride and methanol as eluent. The product gave the following data : NMR ($DMSOd_6$) 2.2 (s, 3H), 3.19 (s, 8H), 3.78 (s, 8H), 7.18 (d, 2H), 7.21 (d, 1H), 7.39 (m, 4H), 7.43 (s, 1H), 7.50 (s, 1H), 7.58 (m, 1H),7.8 (s, 1H), 9.82 (s, 1H), 10.12 (s, 1H); Mass M+H 501.

yy) The reactants were benzoyl chloride and N-(5-amino-2-methylphenyl)-3-(4-methylpiperazin-1-ylmethyl)benzamide. On completion of the reaction, the reaction mixture was washed with water and with a saturated aqueous sodium bicarbonate solution. The mixture was evaporated and the residue was triturated under a mixture of diethyl ether and ethyl acetate. The product so obtained gave the following data : Mass M+H 443.

The N-(5-amino-2-methylphenyl)-3-(4-methylpiperazin-1-ylmethyl)benzamide used as starting material was prepared as follows :-

3-Chloromethylbenzoyl chloride (24.8 ml) was added to a stirred mixture of 2-methyl-5-nitroaniline (26.6 g), triethylamine (49 ml) and methylene chloride (800 ml) and the mixture was stirred at ambient temperature for 16 hours. The precipitate was isolated, washed with 1N aqueous hydrochloric acid solution and with diethyl ether and dried under vacuum at 40°C. There was thus obtained 3-chloromethyl-N-(2-methyl-5-nitrophenyl)benzamide (43.5 g); NMR ($DMSOd_6$) 2.38 (s, 3H), 2.85 (s, 2H), 7.53-7.58 (m, 2H), 7.67 (d, 1H), 7.95(d, 1H), 8.01-8.04 (m, 2H), 8.32 (s, 1H), 10.19 (s, 1H); Mass $M+H^+$ 305.

1-Methylpiperazine (8.03 ml) was added to a stirred mixture of a portion (20 g) of the material so obtained, potassium carbonate (18.2 g) and acetone (750 ml) and the mixture was heated to 54°C and stirred for 16 hours. The resultant solution was

evaporated and the residue was dissolved in methylene chloride. The organic solution was washed with water and evaporated. There was thus obtained N-(2-methyl-5-nitrophenyl)-3-(4-methylpiperazin-1-ylmethyl)benzamide (26.4 g); NMR ($DMSOd_6$) 2.06 (s, 3H), 2.12 (s, 3H), 2.31-2.37 (m, 8H), 3.52 (s, 2H), 7.48-7.57 (m, 3H), 7.87 (d, 2H), 8.01 (m, 1H), 8.33 (s, 1H); Mass $M+H^+$ 369.

Iron powder was added to a stirred mixture of a portion (18.0 g) of the material so obtained, ethanol (500 ml), water (50 ml) and acetic acid (10 ml). The resultant mixture was stirred and heated to reflux for 5 hours. Water (50 ml) was added and the mixture was basified by the addition of sodium carbonate. The mixture was filtered and the filtrate was evaporated to dryness. The residue was triturated under water and the resultant solid was isolated and dried under vacuum at 40°C. There was thus obtained N-(5-amino-2-methylphenyl)-3-(4-methylpiperazin-1-ylmethyl)benzamide (11.1 g); NMR ($DMSOd_6$) 2.03 (s, 3H), 2.13 (s, 3H), 2.24-2.4 (m, 8H), 3.5 (s, 2H), 4.86 (s, 2H) 6.35 (d, 1H), 6.57 (s, 1H), 6.86 (d, 1H), 7.40-7.48 (m, 2H), 7.78-7.83 (m, 2H), 9.57 (s, 1H); Mass $M+H^+$ 339.

zz) The variation of the work-up described in Note yy) was used. The product so obtained gave the following data : Mass M+H 511.

aaa) The variation of the work-up described in Note yy) was used. The product so obtained gave the following data : Mass M+H 461.

bbb) The variation of the work-up described in Note yy) was used. The product so obtained gave the following data : Mass M+H 461.

ccc) The variation of the work-up described in Note yy) was used. The product so obtained gave the following data : Mass M+H 477.

ddd) The variation of the work-up described in Note yy) was used. The product so obtained gave the following data : Mass M+H 477.

eee) The following variation of the procedure of Example 6 was used. A mixture of 4-chlorobenzoyl chloride (0.4 mmol), N-(5-amino-2-methylphenyl)-3-(4-methylpiperazin-1-ylmethyl)benzamide (0.44 mmol) and pyridine (5 ml) was stirred and heated to 70°C for 16 hours. The resultant mixture was evaporated and the residue was partitioned between methylene chloride and a saturated aqueous sodium bicarbonate solution. The organic phase was evaporated and the residue was triturated

under ethyl acetate. The product so obtained gave the following data : NMR ($DMSOd_6$) 2.13 (s, 3H), 2.19 (s, 3H), 2.25-2.37 (m, 8H), 3.51 (s, 2H), 7.22 (d, 1H), 7.45-7.51 (m, 2H), 7.54-7.59 (m, 3H), 7.81-7.87 (m, 3H), 7.97 (d, 2H), 9.88 (s, 1H), 10.28 (s, 1H); Mass M+H 477.

fff) An analogous procedure to that described in Note eee) was used. The product so obtained gave the following data : NMR ($DMSOd_6$) 2.13 (s, 3H), 2.19 (s, 3H), 2.25-2.37 (m, 8H), 3.51 (s, 2H), 7.22 (d, 1H), 7.38-7.58 (m, 6H), 7.75 (s, 1H), 7.85 (d, 2H), 9.88 (s, 1H), 10.44 (s, 1H); Mass M+H 479.

ggg) The variation of the work-up described in Note yy) was used. The product so obtained gave the following data : Mass M+H 479.

hhh) The variation of the work-up described in Note yy) was used. The product so obtained gave the following data : Mass M+H 511.

iii) The variation of the work-up described in Note yy) was used. The product so obtained gave the following data : Mass M+H 511.

jjj) An analogous procedure to that described in Note eee) was used. The product so obtained gave the following data : NMR ($DMSOd_6$) 2.14 (s, 3H), 2.17 (s, 3H), 2.25-2.4 (m, 8H), 3.51 (s, 2H), 3.88 (s, 3H), 7.05 (t, 1H), 7.14-7.22 (m, 2H), 7.45-7.5 (m, 4H), 7.62 (d, 1H),7.78 (s, 1H), 7.85 (d, 2H), 9.9 (s, 1H), 10.06 (s, 1H); Mass M+H 473.

kkk) The variation of the work-up described in Note yy) was used. The product so obtained gave the following data : Mass M+H 473.

lll) The variation of the work-up described in Note yy) was used. The product so obtained gave the following data : Mass M+H 487.

mmm) The variation of the work-up described in Note yy) was used. The product so obtained gave the following data : Mass M+H 503.

nnn) The variation of the work-up described in Note yy) was used. The product so obtained gave the following data : Mass M+H 468.

ooo) The variation of the work-up described in Note yy) was used. The product so obtained gave the following data : Mass M+H 501.

ppp) The reactants were 3-morpholinobenzoyl chloride and N-(5-amino-2-methylphenyl)-3-(4-methylpiperazin-1-ylmethyl)benzamide. On completion of the reaction, the

reaction mixture was washed with water and with a saturated aqueous sodium bicarbonate solution. The mixture was evaporated and the residue was purified by column chromatography on an ion exchange column (isolute SCX column from International Sorbent Technology Limited, Hengoed, Mid-Glamorgan, UK) using a 99:1 mixture of methanol and a saturated aqueous ammonium hydroxide solution as eluent. The product so obtained gave the following data : NMR ($DMSOd_6$) 2.13 (s, 3H), 2.19 (s, 3H), 2.31-2.38 (m, 8H), 3.15-3.18 (m, 4H), 3.52 (s, 2H), 3.73-3.76 (m, 4H), 7.1-7.14 (m, 1H). 7.2 (d, 1H). 7.22-7.38 (m, 2H), 7.4-7.52 (m, 3H). 7.52-7.6 (m, 1H), 7.4-7.87 (m, 2H), 9.84 (s, 1H) 10.11 (s, 1H); Mass M+H 528.

Example 10

N-[5-(4-hydroxybenzamido)-2-methylphenyl]-3,4-dimethoxybenzamide

10% Palladium-on-carbon (0.5 g) was added to a stirred suspension of N-[5-(4-benzyloxybenzamido)-2-methylphenyl]-3,4-dimethoxybenzamide (3.97 g) in methanol (500 ml) and the mixture was stirred under an atmosphere of hydrogen . After cessation of hydrogen uptake, the mixture was filtered and the filtrate was evaporated. The solid so obtained was washed with diethyl ether and dried under vacuum at 60°C. There was thus obtained the title compound (2.93 g), m.p. 258-259°C;

NMR Spectrum: ($DMSOd_6$) 2.17 (s, 3H), 3.83 (s, 6H), 6.84 (d, 2H), 7.05 (d, 1H), 7.19 (d, 1H), 7.54 (m, 2H), 7.65 (d, 1H), 7.78 (d, 1H), 7.84 (d, 2H), 9.74 (br s, 1H), 9.93 (br s, 1H);

Mass Spectrum: $M-H^-$ 405.

Elemental Analysis: Found C, 66.9; H, 5.3; N, 6.7;

$C_{23}H_{22}N_2O_5.0.2H_2O$ requires C, 67.4; H, 5.5; N, 6.8%.

Example 11

N-[5-(3-hydroxybenzamido)-2-methylphenyl]-3,4-dimethoxybenzamide

Using an analogous procedure to that described in Example 10, N-[5-(3-benzyloxybenzamido)-2-methylphenyl]-3,4-dimethoxybenzamide was hydrogenolysed to give the title compound in 72% yield; m.p. 182-183°C;

NMR Spectrum: ($DMSOd_6$) 2.17 (s, 3H), 3.83 (s, 6H), 6.95 (m, 1H), 7.06 (d, 1H), 7.22 (d, 1H), 7.32 (m, 2H), 7.36 (d, 1H), 7.55 (m, 2H), 7.63 (m, 1H), 7.82 (d, 1H), 9.68 (br s, 2H),

9.75 (br s, 1H), 10.13 (br s, 1H); Mass Spectrum: M-H$^-$ 405.

Example 12

N-[5-(3-dimethylaminobenzamido)-2-methylphenyl]-4-acetylbenzamide

4-Acetylbenzoic acid (0.164 g) was added to a stirred mixture of N-(3-amino-4-methylphenyl)-3-dimethylaminobenzamide (0.135 g), diisopropylethylamine (0.325 ml), 2-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate(V) (0.39 g) and DMF (10 ml) and the mixture was stirred at ambient temperature for 16 hours. The resultant solution was evaporated. The residue was dissolved in methylene chloride and the solution was washed in turn with water, a saturated aqueous solution of sodium bicarbonate and brine, dried ($MgSO_4$) and evaporated. The residue was triturated under a mixture of ethyl acetate and isohexane. The resultant solid was isolated, washed with ethyl acetate and dried under vacuum at 40°C. There was thus obtained the title compound as a solid (0.091 g); NMR Spectrum: ($DMSO_6$) 2.19 (s, 3H), 2.63 (s, 3H), 2.95 (s, 6H), 6.91 (d, 1H), 7.29 (m, 4H), 7.62 (d, 1H), 7.82 (s, 1H), 8.1 (m, 4H), 10.12 (s, 1H), 10.13 (s, 1H); Mass Spectrum: M+H$^+$ 416.

Example 13

N-[5-(3-aminobenzamido)-2-methylphenyl]-3,4-dimethoxybenzamide

10% Palladium-on-carbon (0.13 g) was added to a stirred solution of N-[5-(3-nitrobenzamido)-2-methylphenyl]-3,4-dimethoxybenzamide (1.27 g) in methanol (150 ml) and the mixture was stirred under an atmosphere pressure of hydrogen. After cessation of hydrogen uptake, the catalyst was removed by filtration and the filtrate was evaporated. The residue was washed with diethyl ether and dried under vacuum at 60°C. There was thus obtained the title compound (1.02 g), m.p. 179-180°C;
NMR Spectrum: ($DMSOd_6$) 2.15 (s, 3H), 3.82 (s, 6H), 5.25 (s, 2H), 6.72 (d, 1H), 7.05 (br m, 3H), 7.1 (t, 1H), 7.19 (d, 1H), 7.52 (m, 1H), 7.55 (d, 1H), 7.63 (m, 1H), 7.79 (d, 1H), 9.76 (br s, 1H), 10.02 (br s, 1H); Mass spectrum: M+H$^+$ 406;
Elemental Analysis: Found C, 66.3; H, 5.3; N, 9.9;
$C_{23}H_{23}N_3O_4$.0·5H2O requires C, 66.7; H, 5.8; N, 10.1%.

Example 14

N-[5-(3-dimethylaminobenzamido)-2-methylphenyl]-4-carboxybenzamide

A 2N sodium hydroxide solution (0.27 ml)was added to a stirred suspension of N-[5-(3-dimethylaminobenzamido)-2-methylphenyl]-4-methoxycarbonylbenzamide (0.077 g) in a mixture of methanol (10 ml) and water (2 ml). The reaction mixture was stirred at ambient temperature for 16 hours. The mixture was evaporated and the residue was dissolved in water. The aqueous solution was and extracted with ethyl acetate, acidified to pH 5 by the addition of dilute hydrochloric acid and extracted with ethyl acetate. The resultant organic extract was evaporated and the residue was dried at 40°C. There was thus obtained the title compound (0.006 g); Mass Spectrum: $M-H^-$ 416.

Example 15

N-[5-(4-morpholinomethylbenzamido)-2-methylphenyl]-3,4-dimethoxybenzamide

Morpholine (0.03 ml) was added to a stirred suspension of N-[5-(4-chloromethylbenzamido)-2-methylphenyl]-3,4-dimethoxybenzamide (0.15 g) and potassium carbonate (0.094 g) in acetone (10 ml). The mixture was heated to 54°C and stirred for 16 hours. The resultant solution was evaporated and the residue was dissolved in methylene chloride. The organic solution was washed with water and evaporated. The residue was triturated under a mixture of ethyl acetate and diethyl ether. The resultant white solid was isolated and dried under vacuum at 40°C. There was thus obtained the title compound (0.135 g); NMR Spectrum: ($DMSOd_6$) 2.18 (s, 3H), 2.35 (t, 2H), 3.28 (s, 2H), 3.55 (t, 4H), 3.82 (s, 6H), 7.07 (d, 1H), 7.21 (d, 1H), 7.43 (d, 2H), 7.55 (m, 2H), 7.61 (d, 1H), 7.81 (s, 1H), 7.89 (d, 2H), 9.78 (s, 1H), 10.16 (s, 1H); Mass Spectrum: $M+H^+$490.

The N-[5-(4-chloromethylbenzamido)-2-methylphenyl]-3,4-dimethoxybenzamide used as a starting material was prepared as follows :-

4-Chloromethylbenzoyl chloride (0.73 g) was added dropwise to a stirred mixture of N-(5-amino-2-methylphenyl)-3,4-dimethoxybenzamide (1 g), triethylamine (0.98 ml) and methylene chloride (80 ml) and the mixture was stirred at ambient temperature for 16 hours. A 1N hydrochloric acid solution (10 ml) was added and the resultant solution was stirred at ambient temperature for 1 hour. The resultant white solid was filtered off, washed with water and with diethyl ether, dried under vacuum at 40°C to give the required starting material

(1.35 g); NMR Spectrum: ($DMSOd_6$) 2.18 (s, 3H), 3.82 (s, 6H), 4.82 (s, 2H), 7.06 (d, 1H), 7.21 (d, 1H), 7.58 (m, 5H), 7.81 (s, 1H), 7.94 (d, 2H), 9.76 (s, 1H), 10.23 (s, 1H); Mass Spectrum: $M+H^+$ 439.

Example 16

N-{5-[3-(4-methylpiperazin-1-ylmethyl)benzamido]-2-methylphenyl}-3,4-dimethoxybenzamide

Using an analogous procedure to that described in Example 15, 1-methylpiperazine was reacted with N-[5-(3-chloromethylbenzamido)-2-methylphenyl]-3,4-dimethoxybenzamide to give the title compound in 17% yield; NMR Spectrum: ($DMSOd_6$) 2.14 (s, 3H), 2.18 (s, 3H), 2.36 (m, 8H), 3.51 (s, 2H), 3.82 (s, 6H), 7.07 (d, 1H), 7.22 (d, 1H), 7.47 (m, 2H), 7.61 (m, 3H), 7.82 (m, 3H), 9.75 (s, 1H), 10.18 (s, 1H); Mass Spectrum: $M+H^+$ 503.

The N-[5-(3-chloromethylbenzamido)-2-methylphenyl]-3,4-dimethoxybenzamide used as a starting material was prepared as follows :-

3-Chloromethylbenzoyl chloride (0.6 g) was added to a stirred mixture of N-(5-amino-2-methylphenyl)-3,4-dimethoxybenzamide (1 g), triethylamine (0.98 ml) and methylene chloride (100 ml) and the resultant mixture was stirred at ambient temperature for 16 hours. The mixture was washed with 1N hydrochloric acid and with a saturated aqueous solution of sodium bicarbonate, dried ($MgSO_4$) and evaporated. The residue was triturated under a mixture of ethyl acetate and diethyl ether. The resultant white solid was isolated and dried under vacuum at 40°C to give the required starting material (1.35 g); NMR Spectrum: 2.19 (s, 3H), 3.82 (s, 6H), 4.84 (s, 2H), 7.06 (d, 1H), 7.23 (d, 1H), 7.57 (m, 5H), 7.8 (s, 1H), 7.9 (d, 1H), 8.0 (s, 1H), 9.76 (s, 1H), 10.26 (s, 1H); Mass Spectrum: $M+H^+$ 439.

Example 17

N-[5-(3-cyclohexylpropionamido)-2-methylphenyl]-4-methoxybenzamide

4-Methoxybenzoyl chloride (0.064 ml) was added to a stirred mixture of N-(3-amino-4-methylphenyl)-3-cyclohexylpropionamide (J. Med. Chem., 1996, 39, 3343-3356; 0.13 g), triethylamine (0.14 ml) and methylene chloride (5 ml) and the mixture was stirred at ambient temperature for 16 hours. The resultant mixture was washed in turn with a 5% aqueous citric acid solution, with a saturated aqueous solution of sodium bicarbonate and

with brine, dried ($MgSO_4$) and evaporated. The residue was triturated under a mixture of ethyl acetate and isohexane. The resultant solid was isolated and dried under vacuum at 40°C. There was thus obtained the title compound (0.159 g); NMR Spectrum: ($DMSOd_6$) 0.89 (m, 2H), 1.19 (m, 4H), 1.47 (m, 2H), 1.66 (m, 5H), 2.13 (s, 3H), 2.3 (t, 2H), 3.82 (s, 3H), 7.03 (d, 2H), 7.12 (d, 1H), 7.37 (d, 1H), 7.61 (s, 1H), 7.93 (d, 2H), 9.67 (s, 1H), 9.8 (s, 1H); Mass Spectrum: $M+H^+$ 395.

Example 18

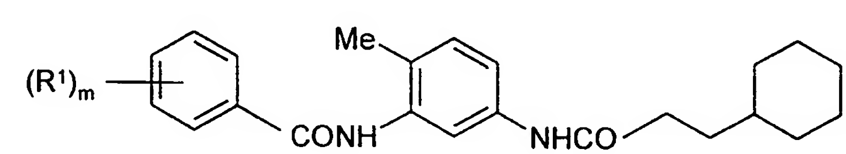
N-[5-(3-cyclohexylpropionamido)-2-methylphenyl]-4-acetylbenzamide

A solution of oxalyl chloride (0.1ml) in methylene chloride (0.5 ml) was added to a stirred mixture of 4-acetylbenzoic acid (0.098 g), DMF (3 drops) and methylene chloride (2 ml). The reaction mixture was stirred and heated to 40°C for 3 hours. The mixture was evaporated to dryness. The residue was dissolved in methylene chloride (2 ml). DMF (3 drops) was added, followed by the addition of a mixture of N-(3-amino-4-methylphenyl)-3-cyclohexylpropionamide (0.138 g) and pyridine (0.2 ml) in methylene chloride (4 ml). The resultant mixture was stirred at ambient temperature for 18 hours. The reaction mixture was evaporated and the residue was triturated under ethyl acetate. The resultant solid was washed with water and dried to give the title product (0.153 g); NMR Spectrum: ($DMSOd_6$) 0.8 (m, 2H), 1.1 (m, 4H), 1.39 (m, 2H), 1.60 (m, 5H) 2.08 (s, 3H), 2.2 (t, 2H), 2.53 (s, 3H), 7.06 (d, 1H), 7.28 (m, 1H), 7.56 (d, 1H), 7.86 (m, 1H), 7.97 (s, 4H), 8.37 (m, 1H), 8.77 (m, 1H), 9.74 (s, 1H), 9.92 (s, 1H); Mass Spectrum: $M+H^+$ 407.

Example 19

Using an analogous procedure to that described in Example 17 or Example 18, the appropriate benzoyl chloride was reacted with the appropriate aniline to give the compounds described in Table II.

Table II



No.	$(R^1)_m$	Method	Note
1	4-ethoxy	Ex. 17	a
2	4-butoxy	Ex. 18	b
3	3,4-dimethoxy	Ex. 17	c
4	3,5-dimethoxy	Ex. 18	d
5	3,4-diethoxy	Ex. 17	e
6	3,4,5-trimethoxy	Ex. 17	f
7	3-methoxycarbonyl	Ex. 18	g
8	3-cyano	Ex. 18	h
9	4-cyano	Ex. 17	i
10	3-methoxy-4-hydroxy	Ex. 18	j
11	2-nitro-4-methoxy	Ex. 18	k

Notes

a) The product gave the following data : NMR ($DMSOd_6$) 0.9 (m, 2H), 1.2 (m, 4H), 1.37 (t, 3H), 1.5 (m, 2H), 1.7 (m, 5H) 2.17 (s, 3H), 2.28 (t, 2H), 4.12 (m, 2H), 7.03 (d, 2H), 7.14 (d, 1H), 7.38 (m, 1H), 7.64 (d, 1H), 7.95 (d, 2H), 9.65 (s, 1H), 9.8 (s, 1H); Mass M+H 409.

b) 4-Dimethylaminopyridine (0.15 equivalents) was added to catalyse the reaction. The product gave the following data : NMR ($DMSOd_6$) 0.89 (m, 5H), 1.12 (m, 4H), 1.53 (m, 11H), 2.32 (s, 3H), 2.28 (t, 2H), 4.02 (t, 2H), 7.0 (d, 2H), 7.12 (d, 1H), 7.38 (d, 1H), 7.60 (s, 1H), 7.9 (d, 2H), 9.64 (s, 1H), 9.78 (s, 1H) ; Mass M+H 437.

c) The product gave the following data : NMR ($DMSOd_6$) 0.89 (m, 2H), 1.19 (m, 4H), 1.45 (m, 7H), 2.14 (s, 3H), 2.27 (t, 2H), 3.82 (s, 6H), 7.04 (d, 1H), 7.14 (d, 1H), 7.36 (s, 1H), 7.52 (s, 1H), 7.60 (s, 1H), 7.62 (s, 1H), 9.68 (s, 1H), 9.8 (s, 1H); Mass M+H 425.

d) The product gave the following data : NMR ($DMSOd_6$) 0.8 (m, 2H), 1.1 (m, 4H), 1.42 (m, 2H), 1.6 (m, 5H) 2.08 (s, 3H), 2.23 (t, 2H), 3.75 (s, 6H), 6.62 (t, 1H), 7.08 (m, 3H), 7.3 (m, 1H), 7.56 (d, 1H), 7.88 (t, 1H), 8.38 (m, 1H), 8.79 (m, 1H), 9.73 (s, 1H), 9.76 (s, 1H); Mass M+H 425.

e) The benzoyl chloride was prepared by the dropwise addition of oxalyl chloride (0.75 mmol) to a stirred mixture of 3,4-diethoxybenzoic acid (0.75 mmol) and DMF (a few drops) which had been cooled to 0°C. The mixture was allowed to warm to ambient temperature and was stirred for four hours. The resultant solution was evaporated and the resultant acid chloride was used without further purification. The benzamide product gave the following data : Mass M+H 453.

f) The product gave the following data : NMR ($DMSOd_6$) 0.87 (m, 2H), 1.12 (m, 4H), 1.45 (m, 2H), 1.64 (m, 5H), 2.13 (s, 3H), 2.27 (t, 2H), 3.71 (s, 3H), 3.83 (s, 6H), 7.14 (d, 2H), 7.29 (s, 1H), 7.33 (d, 1H), 7.61 (s, 1H), 9.81 (s, 2H); Mass M+H 455.

g) The product gave the following data : NMR ($DMSOd_6$) 0.9 (m, 2H), 1.15 (m, 4H), 1.49 (m, 2H), 1.65 (m, 5H) 2.18 (s, 3H), 2.28 (t, 2H), 3.92 (s, 3H), 7.17 (d, 1H), 7.38 (m, 1H), 7.68 (m, 2H), 8.15 (d, 1H), 8.24 (d, 1H), 8.57 (s, 1H), 9.84 (s, 1H), 10.1 (s, 1H); Mass M+H 423.

h) The product gave the following data : Mass M+H 390.

i) The product gave the following data : Mass M+H 390.

j) The product gave the following data : NMR ($DMSOd_6$) 0.9 (m, 2H), 1.25 (m, 4H), 1.5 (m, 2H), 1.7 (m, 5H) 2.2 (s, 3H), 2.62 (t, 2H), 3.87 (s, 3H), 6.86 (d, 1H), 7.15 (d, 1H), 7.35 (m, 1H), 7.5 (m, 1H), 7.6 (d, 1H), 7.64 (d, 1H), 9.55 (s, 1H), 9.57 (s, 1H), 9.75 (s, 1H); Mass M+H 411.

k) The product gave the following data : Mass M+H 439.

Example 20

N-[5-(3-cyclohexylpropionamido)-2-methylphenyl]-4-carboxybenzamide

A 2N sodium hydroxide solution (0.27 ml) was added to a stirred suspension of N-[5-(3-cyclohexylpropionamido)-2-methylphenyl]-4-methoxycarbonylbenzamide (0.087 g) in a mixture of methanol (10 ml) and water (2 ml). The reaction mixture was stirred at ambient temperature for 16 hours. The mixture was evaporated and the residue was dissolved in water. The aqueous solution was and extracted with ethyl acetate, acidified to pH 5 by the addition of dilute hydrochloric acid and extracted with ethyl acetate. The resultant organic extract was evaporated and the residue was dried at 40°C. There was thus obtained the title compound (0.016 g); NMR Spectrum: ($DMSOd_6$) 0.91 (m, 2H), 1.16 (m, 4H), 1.47 (m, 2H),

1.66 (m, 5H), 2.15 (s, 3H), 2.28 (t, 2H), 7.15 (d, 1H), 7.36 (d, 1H), 7.64 (s, 1H), 8.06 (d, 4H), 9.82 (s, 1H), 10.04 (s, 1H); Mass Spectrum: M-H$^-$ 407.

The N-[5-(3-cyclohexylpropionamido)-2-methylphenyl]-4-methoxycarbonylbenzamide used as a starting material was obtained as follows :-

4-Methoxycarbonylbenzoyl chloride (0.198 g) was added to a stirred mixture of N-(3-amino-4-methylphenyl)-3-cyclohexylpropionamide (0.13 g), 4-dimethylaminopyridine (0.06 g), triethylamine (0.139 ml) and methylene chloride (10 ml) and the mixture was stirred at ambient temperature for 16 hours. The resultant precipitate was filtered off and washed in turn with methylene chloride, ethyl acetate and 1N hydrochloric acid. The solid was dried under vacuum at 40°C to give the title product (0.105 g); NMR Spectrum: ($DMSOd_6$) 0.78 (m, 2H), 1.14 (m, 4H), 1.25 (m, 2H), 1.53 (m, 5H), 2.15 (s, 3H), 2.28 (t, 2H), 3.88 (s. 3H), 7.15 (d, 1H), 7.37 (d 2H), 7.64 (s, 1H), 8.07 (s, 4H), 9.82 (s, 1H), 10.05 (s, 1H); Mass Spectrum: M+H$^-$ 432

Example 21

N-[5-(3-cyclohexylpropionamido)-2-methylphenyl]-3-carboxybenzamide

Using an analogous procedure to that described in Example 20, N-[5-(3-cyclohexylpropionamido)-2-methylphenyl]-3-methoxycarbonylbenzamide was hydrolysed to give the title compound in 16% yield; Mass Spectrum: M-H$^-$ 407.

Example 22

N-[5-(5-cyclohexylpentanoamido)-2-methylphenyl]-4-hydroxybenzamide

A solution of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.096 g) in methylene chloride (3 ml) was added to a stirred mixture of N-(5-amino-2-methylphenyl)-4-hydroxybenzamide (0.13 g), 5-cyclohexylpentanoic acid (0.092 g) and DMF (0.5 ml) and the reaction mixture was stirred at ambient temperature for 5 hours. The mixture was evaporated and the residue was partitioned between ethyl acetate and 1N hydrochloric acid solution. The organic phase was evaporated to give the title compound (0.083 g); NMR Spectrum: ($DMSOd_6$) 0.85 (m, 2H), 1.2 (m, 8H), 1.65 (m, 7H) 2.15 (s, 3H), 2.28 (t, 2H), 6.86 (d, 2H), 7.14 (d, 1H), 7.3 (m, 1H), 7.62 (d, 1H), 7.86 (d, 2H), 9.54 (s, 1H), 9.77 (s, 1H), 10.01 (s, 1H); Mass Spectrum: M+H$^+$ 409.

Example 23

The following compounds are described in J. Med. Chem., 1996, 39, 3343-3356 and were prepared using analogous procedures. The compounds possess p38 kinase inhibitory activity.

N-[5-(3-cyclopentylpropionamido)-2-methylphenyl]-4-hydroxybenzamide;
N-[5-(3-cyclohexylpropionamido)-2-methylphenyl]-3-hydroxybenzamide;
N-[5-(3-cyclohexylpropionamido)-2-methylphenyl]-4-hydroxybenzamide; and
N-[5-(3-cyclohexylpropionamido)-2-methylphenyl]-4-aminobenzamide.

Example 24

N-[5-(4-Cyclohexylbutyrylamino)-2-methylphenyl]-4-hydroxybenzamide

4-Cyclohexylbutyric acid (255 mg) was added to a solution of N-(5-amino-2-methylphenyl)-4-hydroxybenzamide (242 mg) in DMF (3.0 ml). The mixture was stirred and a solution of 1-(3-dimethylamino)propyl-3-ethylcarbodiimide hydrochloride (287 mg) added. The mixture was stirred overnight at ambient temperature, evaporated to a small volume and ethyl acetate (5 ml) was added. The mixture was washed with aqueous sodium bicarbonate solution (5 ml), water (5 ml), 2M aqueous hydrochloric acid (5 ml), water (5 ml) and brine (5 ml). The organic phase was filtered through a megabond elute column, eluting with ethyl acetate (25 ml) and evaporated to dryness. The residue was triturated with ether, filtered, washed with ether and dried to give the title compound (280 mg), m.p. 159-160°C; NMR Spectrum: ($DMSOd_6$) 0.75-1.0 (m, 2H), 1.05-1.35 (m, 6H), 1.5-1.78 (m, 7H), 2.18 (s, 3H), 2.27 (t, 2H), 6.86 (d, 2H), 7.14 (d, 1H), 7.39 (m, 1H), 7.63 (d, 1H), 7.86 (d, 2H), 9.56 (s, 1H), 9.7 (s, 1H), 10.0 (s, 1H); Mass Spectrum: $M+H^+$ 395, $(M+Na)^+$ 417;

Microanalysis: % Theory C 73.1, H 7.66, N 7.1%,
% Found C 73.3, H 7.7, N 7.0%.

Example 25

N-[2-methyl-5-(3-trifluoromethylbenzamido)phenyl]-3,4-dimethoxybenzamide

Phosphoryl chloride (0.045 ml) was added to a stirred solution of N-(3-amino-4-methylphenyl)-3-trifluoromethylbenzamide (0.119 g) and 3,4-dimethoxybenzoic acid (0.088 g) in pyridine (1 ml) which had been cooled to 0°C. The mixture was allowed to warm

to ambient temperature and was stirred for 16 hours. The resultant mixture was poured into a 2N aqueous hydrochloric acid solution. The resultant solid was isolated, washed with a saturated aqueous sodium bicarbonate solution and with isohexane and dried under vacuum at 55°C. There was thus obtained the title compound (0.107 g); NMR Spectrum: ($DMSOd_6$) 2.2 (s, 3H), 3.82 (s, 6H), 7.07 (d, 1H), 7.23 (d, 1H), 7.60 (m, 3H), 7.77 (m, 2H), 7.95 (d, 1H), 8.27 (m, 2H), 9.76 (s, 1H), 10.43 (s, 1H); Mass Spectrum: $M-H^-$ 457.

The N-(3-amino-4-methylphenyl)-3-trifluoromethylbenzamide used as starting material was prepared by the reaction of 3-trifluoromethylbenzoyl chloride with 4-methyl-3-nitroaniline and reduction of the resultant product using analogous procedures to those described in the portion of Example 8 which is concerned with the preparation of starting materials.

Example 26

N-[5-(3-morpholinomethylbenzamido)-2-methylphenyl]-3,4-dimethoxybenzamide

Using an analogous procedure to that described in Example 15, morpholine was reacted with N-[5-(3-chloromethylbenzamido)-2-methylphenyl]-3,4-dimethoxybenzamide to give the title compound in 84% yield; NMR Spectrum: ($DMSOd_6$) 2.18 (s, 3H), 2.37 (t, 4H), 3.52 (s, 2H), 3.56 (t, 4H), 3.82 (s, 6H), 7.07 (d, 1H), 7.21 (d, 1H), 7.43-7.59(m, 2H), 7.52-7.64 (m, 3H), 7.79 (s, 1H), 7.89 (d, 2H), 9.78 (s, 1H), 10.16 (s, 1H); Mass Spectrum: $M+H^+$ 490.

Example 27

N-[5-(4-cyanobenzamido)-2-methylphenyl]-4-morpholinomethylbenzamide

A mixture of N-[5-(4-cyanobenzamido)-2-methylphenyl]-4-chloromethylbenzamide (0.1 g), morpholine (0.033 g), potassium carbonate (0.068 g) and acetone (5 ml) was stirred and heated to 55°C for 16 hours. The reaction mixture was evaporated and the residue was triturated under water. The solid so obtained was isolated and dried under vacuum at 55°C. There was thus obtained the title compound (0.099 g); NMR Spectrum: ($DMSOd_6$) 2.2 (s, 3H), 2.38 (m, 4H), 3.52 (s, 2H), 3.58 (t, 4H), 7.23 (d, 1H), 7.45 (d, 2H), 7.57 (d, 1H), 7.82 (d, 1H), 7.93 (d, 2H), 8.0 (d, 2H), 8.1 (d, 2H), 9.85 (s, 1H), 10.45 (s, 1H); Mass Spectrum: $M-H^-$ 453.

The N-[5-(4-cyanobenzamido)-2-methylphenyl]-4-chloromethylbenzamide used as a

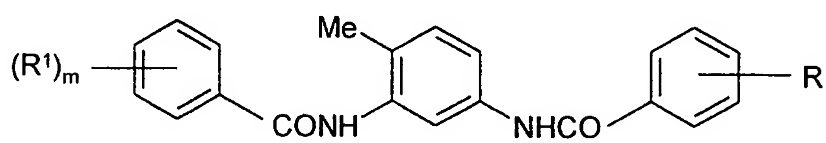
starting material was obtained as follows :-

Triethylamine (1.83 ml) was added to a stirred mixture of N-(3-amino-4-methylphenyl)-4-cyanobenzamide (3.0 g), 4-chloromethylbenzoyl chloride (2.48 g), 4-dimethylaminopyridine (0.146 g) and methylene chloride (50 ml) and the reaction mixture was stirred at ambient temperature for 16 hours. The mixture was evaporated and the residue was triturated under 2N aqueous hydrochloric acid solution. The solid so obtained was isolated, washed in turn with a saturated aqueous sodium bicarbonate solution, water and isohexane and dried under vacuum at 55°C. There was thus obtained the required compound (4.76 g); NMR Spectrum: ($DMSOd_6$) 2.2 (s, 3H), 4.84 (s, 2H), 7.25 (d, 1H), 7.57 (d, 3H), 7.83 (d, 1H), 7.98 (m, 4H), 8.1 (d, 2H), 9.93 (s, 1H), 10.46 (s, 1H);
Mass Spectrum: $M-H^-$ 402.

Example 28

Using an analogous procedure to that described in Example 27, the appropriate amine was reacted with the appropriate benzyl chloride to give the compounds described in Table III.

Table III



No.	$(R^1)_m$	R	Note
1	3-(piperazin-1-yl)methyl	hydrogen	a
2	3-(4-propylpiperazin-1-yl)methyl	hydrogen	b
3	3-(4-carbamoylpiperidin-1-yl)methyl	hydrogen	c
4	4-(4-methylhomopiperazin-1-yl)methyl	hydrogen	d
5	3-(4-acetylpiperazin-1-yl)methyl	3-trifluoromethyl	e
6	4-(4-ethylpiperazin-1-yl)methyl	3-trifluoromethyl	f
7	4-(4-methylpiperazin-1-yl)methyl	4-cyano	g
8	3-(4-isopropylpiperazin-1-yl)methyl	4-cyano	h

No.	$(R^1)_m$	R	Note
9	3-(pyrrolidin-1-yl)methyl	4-cyano	i
10	3-morpholinomethyl	4-cyano	j
11	4-piperidinomethyl	4-cyano	k
12	4-(piperazin-1-yl)methyl	4-cyano	l
13	4-(4-methylpiperazin-1-yl)methyl	4-cyano	m

Notes

a) The product gave the following data : NMR ($DMSOd_6$) 2.2 (s, 3H), 2.3 (m, 4H), 2.67 (m, 4H), 3.48 (s, 2H), 7.21 (d, 1H), 7.53 (m, 6H), 7.84 (m, 3H), 7.95 (d, 2H), 9.88 (s, 1H), 10.21 (s, 1H); Mass M-H 428.

The N-(5-benzamido-2-methylphenyl)-3-chloromethylbenzamide used as a starting material was prepared as follows :

Triethylamine (2.0 ml) was added to a stirred mixture of N-(3-amino-4-methylphenyl)benzamide (3.0 g), 3-chloromethylbenzoyl chloride (2.76 g), 4-dimethylaminopyridine (0.162 g) and methylene chloride (50 ml) and the reaction mixture was stirred at ambient temperature for 16 hours. The mixture was evaporated and the residue was triturated under 2N aqueous hydrochloric acid solution. The solid so obtained was isolated, washed in turn with a saturated aqueous sodium bicarbonate solution, water and isohexane and dried under vacuum at 55°C. There was thus obtained the required compound (5.1 g) which was used without further purification; NMR ($DMSOd_6$) 2.19 (s, 3H), 4.85 (s, 2H), 7.23 (d, 1H), 7.55 (m, 5H), 7.66 (d, 1H), 7.84 (s, 1H), 7.95 (m, 3H), 8.05 (s, 1H), 9.96 (s, 1H), 10.22 (s, 1H); Mass M-H 377.

b) The product gave the following data : NMR ($DMSOd_6$) 0.91 (t, 3H), 1.40 (m, 2H), 2.19 (m, 5H), 2.37 (br s, 8H), 3.53 (s, 2H), 7.21 (d, 1H), 7.52 (m, 6H), 7.84 (m, 3H), 7.95 (d, 2H); Mass M-H 469.

c) The product gave the following data : NMR ($DMSOd_6$) 1.6 (m, 4H), 1.98 (m, 3H), 2.2 (s, 3H), 2.82 (br d, 2H), 3.51 (s, 2H), 6.65 (br s, 1H), 7.17 (br s, 1H), 7.21 (d, 1H), 7.52 (m, 6H), 7.83 (m, 3H), 7.95 (d, 2H); Mass M-H 469.

d) The product gave the following data : NMR ($DMSOd_6$) 1.7 (m, 2H), 2.2 (s, 3H), 2.24 (s, 3H), 2.58 (m, 8H), 3.66 (s, 2H), 7.21 (d, 1H), 7.52 (m, 6H), 7.83 (m, 1H), 7.95

(m, 4H); Mass M-H 455.

The N-(5-benzamido-2-methylphenyl)-4-chloromethylbenzamide used as a starting material was prepared as follows :

Triethylamine (2.0 ml) was added to a stirred mixture of N-(3-amino-4-methylphenyl)benzamide (3.0 g), 4-chloromethylbenzoyl chloride (2.76 g) 4-dimethylaminopyridine (0.162 g) and methylene chloride (50 ml) and the reaction mixture was stirred at ambient temperature for 16 hours. The mixture was evaporated and the residue was triturated under 2N aqueous hydrochloric acid solution. The solid so obtained was isolated, washed in turn with a saturated aqueous sodium bicarbonate solution, water and isohexane and dried under vacuum at 55°C. There was thus obtained the required compound (4.96 g); NMR ($DMSOd_6$) 2.19 (s, 3H), 4.84 (s, 2H), 7.22 (d, 1H), 7.54 (m, 6H), 7.84 (s, 1H), 7.96 (m, 4H), 9.92 (s, 1H), 10.22 (s, 1H); Mass M-H 377.

e) The product gave the following data : NMR ($DMSOd_6$) 1.97 (s, 3H), 2.2 (s, 3H), 2.38 (m, 4H), 3.28 (br s, 2H), 3.42 (br s, 2H), 3.56 (s, 2H), 7.22 (d, 1H), 7.5 (m, 3H), 7.75 (t, 1H), 7.81 (s, 1H), 7.91 (m, 3H), 8.28 (m, 2H); Mass M-H 537.

The N-[5-(3-trifluoromethylbenzamido)-2-methylphenyl]-3-chloromethylbenzamide used as a starting material was prepared as follows :

A mixture of 3-trifluoromethylbenzoyl chloride (9.9 ml), 3-nitro-4-methylaniline (10 g) and pyridine (100 ml) was stirred and heated to 80°C for 2 hours. The reaction mixture was evaporated and the residue was triturated under 2N aqueous hydrochloric acid solution. The solid so obtained was isolated, washed in turn with a saturated aqueous sodium bicarbonate solution, water and isohexane and dried under vacuum at 55°C to give N-(4-methyl-3-nitrophenyl)-3-trifluoromethylbenzamide as a solid (21.9 g); NMR ($DMSOd_6$) 7.49 (d, 1H), 7.78 (m, 1H), 7.99 (m, 2H), 8.27 (m, 2H), 8.51 (s, 1H), 10.77 (s, 1H); Mass M-H 323.

Palladium on charcoal (1.0 g) was added to a solution of a portion (10 g) of the material so obtained in methanol (250 ml). Ammonium formate (19.0 g) was added and the resultant mixture was stirred and heated to reflux for 1 hour. The mixture was filtered through diatomaceous earth (Celite®) and the filtrate was evaporated. The residue was triturated under water. The resultant solid was isolated and dried under

vacuum at 55°C to give N-(3-amino-4-methylphenyl)-3-trifluoromethylbenzamide as a solid (7.98 g); NMR ($DMSOd_6$) 2.01 (s, 3H), 4.83 (s, 2H), 6.85 (m, 2H), 7.08 (s, 1H), 7.74 (t, 1H), 7.92 (d, 1H), 8.2 (d, 1H), 10.11 (s, 1H); Mass M-H 293.

Triethylamine (1.6 ml) was added to a stirred mixture of a portion (3.0 g) of the material so obtained, 3-chloromethylbenzoyl chloride (2.17 ml), 4-dimethylaminopyridine (0.125 g) and methylene chloride (50 ml) and the reaction was stirred at ambient temperature for 16 hours. The mixture was evaporated and the residue was triturated under 2N aqueous hydrochloric acid solution. The solid so obtained was isolated, washed in turn with a saturated aqueous sodium bicarbonate solution, water and isohexane and dried under vacuum at 55°C. There was thus obtained the required compound as a solid (5.17 g); NMR ($DMSOd_6$) 2.2 (s, 3H), 4.85 (s, 2H), 7.25 (d, 1H), 7.6 (m, 3H), 7.8 (m, 2H), 7.95 (d, 2H), 8.05 (s, 1H), 8.16 (m, 2H), 9.96 (s, 1H), 10.44 (s, 1H); Mass M-H 445.

f) The product gave the following data : NMR ($DMSOd_6$) 0.97 (t, 3H), 2.2 (s, 3H), 2.35 (m, 10H), 3.53 (s, 2H), 7.23 (d, 1H), 7.42 (d, 2H), 7.59 (d, 1H), 7.78 (m, 2H), 7.93 (m, 3H), 8.26 (m, 2H); Mass M-H 524.

The N-[5-(3-trifluoromethylbenzamido)-2-methylphenyl]-4-chloromethylbenzamide used as a starting material was prepared as follows :

Triethylamine (1.6 ml) was added to a mixture of N-(3-amino-4-methylphenyl)-3-trifluoromethylbenzamide (3 g), 4-chloromethylbenzoyl chloride (2.9 g), 4-dimethylaminopyridine (0.125 g) and methylene chloride (50 ml) and the reaction mixture was stirred at ambient temperature for 16 hours. The mixture was evaporated and the residue was triturated under 2N aqueous hydrochloric acid solution. The solid so obtained was isolated, washed in turn with a saturated aqueous sodium bicarbonate solution, water and isohexane and dried under vacuum at 55°C. There was thus obtained the required compound as a solid (5.07 g); NMR ($DMSOd_6$) 2.21 (s, 3H), 4.84 (s, 2H), 7.25 (d, 1H), 7.57 (m, 3H), 7.76 (t, 1H), 7.83 (d, 1H), 7.96 (m, 3H), 8.26 (m, 2H), 9.92 (s, 1H), 10.44 (s, 1H); Mass M-H 445.

g) The product gave the following data : NMR ($DMSOd_6$) 2.14 (s, 3H), 2.2 (s, 3H), 2.36 (m, 8H), 3.51 (s, 2H), 7.23 (d, 1H), 7.46 (m, 2H), 7.58 (m, 1H), 7.84 (m, 3H), 8.0 (d, 2H), 8.1 (d, 2H); Mass M-H 467.

The N-[5-(4-cyanobenzamido)-2-methylphenyl]-3-chloromethylbenzamide used as a starting material was prepared as follows :

Triethylamine (1.83 ml) was added to a mixture of N-(3-amino-4-methylphenyl)-4-cyanobenzamide (3 g), 3-chloromethylbenzoyl chloride (2.48 g), 4-dimethylaminopyridine (0.146 g) and methylene chloride (50 ml) and the reaction mixture was stirred at ambient temperature for 16 hours. The mixture was evaporated and the residue was triturated under 2N aqueous hydrochloric acid solution. The solid so obtained was isolated, washed in turn with a saturated aqueous sodium bicarbonate solution, water and isohexane and dried under vacuum at 55°C. There was thus obtained the required compound as a solid (4.76 g); NMR ($DMSOd_6$) 2.2 (s, 3H), 4.84 (s, 2H), 7.24 (d, 1H), 7.55 (m, 2H), 7.66 (d, 1H), 7.83 (d, 1H), 8.0 (m, 4H), 8.1 (d, 2H), 9.96 (s, 1H), 10.46 (s, 1H); Mass M-H 402.

h) The product gave the following data : NMR ($DMSOd_6$) 0.92 (d, 6H), 2.2 (s, 3H), 2.39 (m, 8H), 2.58 (m, 1H), 3.5 (s, 2H), 7.22 (d, 1H), 7.45 (m, 2H), 7.56 (d, 1H), 7.85 (m, 3H), 8.0 (d, 2H), 8.11 (d, 2H); Mass M-H 494.

The N-[5-(4-cyanobenzamido)-2-methylphenyl]-4-chloromethylbenzamide used as a starting material was prepared by the reaction of N-(3-amino-4-methylphenyl)-4-cyanobenzamide and 4-chloromethylbenzoyl chloride using an analogous procedure to that described in Note g) immediately hereinbefore.

i) The product gave the following data : NMR ($DMSOd_6$) 1.71 (br s, 4H), 2.2 (s, 3H), 2.46 (m, 4H), 3.63 (s, 2H), 7.23 (d, 1H), 7.47 (m, 2H), 7.59 (m, 1H), 7.85 (m, 3H), 7.99 (d, 2H), 8.12 (d, 2H); Mass M-H 437.

j) The product gave the following data : NMR ($DMSOd_6$) 2.2 (s, 3H), 2.38 (m, 4H), 3.52 (s, 2H), 3.58 (t, 4H), 7.13 (d, 1H), 7.5 (m, 3H), 7.85 (m, 3H), 8.0 (d, 2H), 8.1 (d, 2H); Mass M-H 453.

k) The product gave the following data : NMR ($DMSOd_6$) 1.38 (br s, 2H), 1.48 (br s, 4H), 2.2 (s, 3H), 2.32 (br s, 4H), 3.5 (s, 2H), 7.23 (d, 1H), 7.42 (d, 2H), 7.58 (d, 1H), 7.84 (s, 1H), 7.95 (d, 2H), 8.01 (d, 2H), 8.13 (d, 2H), 9.84 (br s, 1H), 10.47 (br s, 1H); Mass M-H 452.

l) The product gave the following data : NMR ($DMSOd_6$) 2.2 (s, 3H), 2.3 (m, 4H), 2.66 (m, 4H), 3.48 (s, 2H), 7.23 (d, 1H), 7.42 (d, 2H), 7.57 (d, 1H), 7.82 (s, 1H), 7.91

(d, 2H), 8.0 (d, 2H), 8.1 (d, 2H), 9.84 (s, 1H), 10.47 (s, 1H); Mass M-H 453.

m) The product gave the following data : NMR (DMSOd_6) 2.12 (s, 3H), 2.19 (s, 3H), 2.36 (m, 8H), 3.51 (s, 2H), 7.22 (d, 1H), 7.42 (d, 2H), 7.58 (m, 1H), 7.81 (d, 1H), 7.92 (d, 2H), 7.99 (d, 2H), 8.1 (d, 2H); Mass M-H 466.

Example 29

N-[5-(2-hydroxybenzamido)-2-methylphenyl]-3,4-dimethoxybenzamide

Using an analogous procedure to that described in Example 10, N-[5-(2-benzyloxybenzamido)-2-methylphenyl]-3,4-dimethoxybenzamide was hydrogenolysed to give the title compound in 92% yield; NMR Spectrum: (DMSOd_6) 2.19 (s, 3H), 3.82 (s, 6H), 6.94 (m, 2H), 7.06 (d, 1H), 7.24 (d, 1H), 7.42 (t, 1H), 7.47 (m, 1H), 7.53 (d, 1H), 7.62 (m, 2H), 7.76 (d, 1H), 7.96 (m, 1H), 9.75 (br s, 1H), 10.35 (br s, 1H), 11.83 (br s, 1H); Mass Spectrum: M-H^- 405.

The N-[5-(2-benzyloxybenzamido)-2-methylphenyl]-3,4-dimethoxybenzamide used as a starting material was obtained by the reaction of N-(5-amino-2-methylphenyl)-3,4-dimethoxybenzamide and 2-benzyloxybenzoyl chloride (obtained by the reaction of 2-benzyloxybenzoic acid and oxalyl chloride) using an analogous procedure to that described in Example 6. There was thus obtained the title compound in 64% yield; NMR Spectrum: (DMSOd_6) 2.13 (s, 3H), 3.83 (s, 6H), 5.24 (s, 2H), 7.11 (m, 3H), 7.26 (m, 3H), 7.52 (m, 4H), 7.63 (m, 2H), 7.71 (m, 1H), 7.86 (t, 2H), 9.73 (br s, 1H), 10.13 (d, 1H); Mass Spectrum: M+H^+ 497.

Example 30

N-[5-(3-dimethylaminobenzamido)-2-methylphenyl]-2-hydroxybenzamide

Using an analogous procedure to that described in Example 10, N-[5-(3-dimethylaminobenzamido)-2-methylphenyl]-2-benzyloxybenzamide was hydrogenolysed to give the title compound in 69% yield, m.p. 234-238°C; NMR Spectrum: (DMSOd_6) 2.22 (s, 3H), 2.97 (s, 6H), 6.92 (m, 3H), 7.21 (m, 3H), 7.3 (m, 1H), 7.42 (m, 1H), 7.57 (m, 1H), 8.02 (m, 1H), 8.21 (d, 1H), 10.15 (s, 1H), 10.38 (m, 1H); Mass Spectrum: M+H^+ 390.

The N-[5-(3-dimethylaminobenzamido)-2-methylphenyl]-2-benzyloxybenzamide used

as a starting material was obtained by the reaction of N-(3-amino-4-methylphenyl)-3-dimethylaminobenzamide and 2-benzyloxybenzoyl chloride using an analogous procedure to that described in Example 7. There was thus obtained the title compound, m.p. 136-139°C; NMR Spectrum: (DMSOd_6) 1.85 (s, 1H), 2.98 (s, 6H), 5.36 (s, 2H), 6.9 (d, 1H), 7.12 (m, 2H), 7.33 (m, 7H), 7.52 (m, 4H), 7.9 (d, 1H), 8.12 (s, 1H), 9.7 (s, 1H), 10.08 (s, 1H); Mass Spectrum: M+H$^+$ 480.

Example 31

N-[5-(3-dimethylaminobenzamido)-2-methylphenyl]-3-aminobenzamide

10% Palladium-on-carbon (0.3 g) was added to a stirred suspension of N-[5-(3-dimethylaminobenzamido)-2-methylphenyl]-3-nitrobenzamide (2.25 g) in methanol (300 ml) and the mixture was stirred under an atmosphere of hydrogen. After cessation of hydrogen uptake, the mixture was filtered and the filtrate was evaporated. The solid so obtained was dried under vacuum at 60°C. There was thus obtained the title compound (1.8 g); NMR Spectrum: (DMSO d_6) 2.18 (s, 3H), 2.95 (s, 6H), 5.26 (br s, 2H), 6.73 (m, 1H), 6.89 (m, 1H), 7.15 (m, 3H), 7.21 (m, 3H), 7.27 (m, 1H), 7.57 (m, 1H), 7.77 (d, 1H), 9.63 (br s, 1H), 10.07 (br s, 1H); Mass Spectrum: M+H$^+$ 390.

Example 32

N-[5-(3-dimethylaminobenzamido)-2-methylphenyl]-3-acetamidobenzamide

Acetyl chloride (0.066 g) was added to a stirred mixture of N-[5-(3-dimethylaminobenzamido)-2-methylphenyl]-3-aminobenzamide (0.3 g), triethylamine (0.22 ml) and methylene chloride (10 ml) and the mixture was stirred at ambient temperature for 60 hours. The mixture was washed with a saturated aqueous sodium bicarbonate solution and with water, dried ($MgSO_4$) and evaporated. The resultant solid was dried under vacuum at 60°C. There was thus obtained the title compound (0.243 g), m.p. 178-179°C;

NMR Spectrum: (DMSO d_6) 2.05 (s, 3H), 2.19 (s, 3H), 2.95 (s, 6H), 6.9 (m, 1H), 7.24 (m, 3H), 7.29 (t, 1H), 7.42 (t, 1H), 7.57 (m, 1H), 7.61 (m, 1H), 7.79 (d, 1H), 7.81 (m, 1H), 8.09 (d, 1H), 9.86 (s, 1H), 10.09 (m, 2H); Mass Spectrum: M+H$^+$ 432.

Example 33

N-[5-(3-acetamidobenzamido)-2-methylphenyl]-3,4-dimethoxybenzamide

Using an analogous procedure to that described in Example 32, acetyl chloride was reacted with N-[5-(3-aminobenzamido)-2-methylphenyl]-3,4-dimethoxybenzamide to give the title compound in 69% yield, m.p. 187-188°C;

NMR Spectrum: ($DMSOd_6$) 2.05 (s, 3H), 2.18 (s, 3H), 3.92 (s, 6H), 7.06 (d, 1H), 7.21 (d, 1H), 7.42 (t, 1H), 7.58 (m, 4H), 7.8 (m, 1H), 8.05 (m, 1H), 9.77 (s, 1H), 10.1 (s, 1H), 10.21 (s, 1H); Mass Spectrum: $M+H^+$ 448.

Example 34

Pharmaceutical compositions

The following illustrate representative pharmaceutical dosage forms of the invention as defined herein (the active ingredient being termed "Compound X"), for therapeutic or prophylactic use in humans:

(a)	Tablet I	mg/tablet
	Compound X	100
	Lactose Ph.Eur	182.75
	Croscarmellose sodium	12.0
	Maize starch paste (5% w/v paste)	2.25
	Magnesium stearate	3.0

(b)	Tablet II	mg/tablet
	Compound X	50
	Lactose Ph.Eur	223.75
	Croscarmellose sodium	6.0
	Maize starch	15.0
	Polyvinylpyrrolidone (5% w/v paste)	2.25
	Magnesium stearate	3.0

(c) Tablet III

Ingredient	mg/tablet
Compound X	1.0
Lactose Ph.Eur	93.25
Croscarmellose sodium	4.0
Maize starch paste (5% w/v paste)	0.75
Magnesium stearate	1.0

(d) Capsule

Ingredient	mg/capsule
Compound X	10
Lactose Ph.Eur	488.5
Magnesium	1.5

(e) Injection I (50 mg/ml)

Compound X	5.0% w/v
1M Sodium hydroxide solution	15.0% v/v
0.1M Hydrochloric acid (to adjust pH to 7.6)	
Polyethylene glycol 400	4.5% w/v
Water for injection to 100%	

(f) Injection II (10 mg/ml)

Compound X	1.0% w/v
Sodium phosphate BP	3.6% w/v
0.1M Sodium hydroxide solution	15.0% v/v
Water for injection to 100%	

(g) Injection III (1mg/ml, buffered to pH6)

Compound X	0.1% w/v
Sodium phosphate BP	2.26% w/v
Citric acid	0.38% w/v
Polyethylene glycol 400	3.5% w/v
Water for injection to 100%	

(h) Aerosol I

	mg/ml
Compound X	10.0
Sorbitan trioleate	13.5
Trichlorofluoromethane	910.0
Dichlorodifluoromethane	490.0

(i) Aerosol II

	mg/ml
Compound X	0.2
Sorbitan trioleate	0.27
Trichlorofluoromethane	70.0
Dichlorodifluoromethane	280.0
Dichlorotetrafluorocthane	1094.0

(j) Aerosol III

	mg/ml
Compound X	2.5
Sorbitan trioleate	3.38
Trichlorofluoromethane	67.5
Dichlorodifluoromethane	1086.0
Dichlorotetrafluoroethane	191.6

(k) Aerosol IV

	mg/ml
Compound X	2.5
Soya lecithin	2.7
Trichlorofluoromethane	67.5
Dichlorodifluoromethane	1086.0
Dichlorotetrafluoroethane	191.6

(l) Ointment

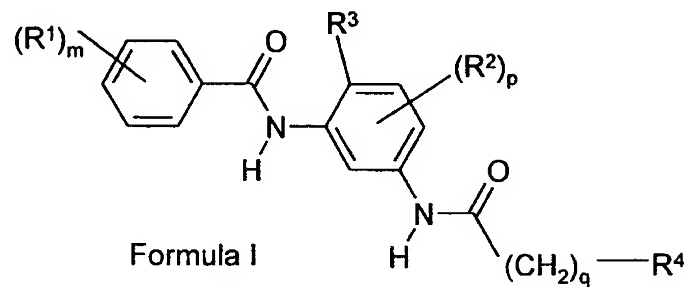
	ml
Compound X	40 mg
Ethanol	300 μl
Water	300 μl
1-Dodecylazacycloheptan-2-one	50 μl
Propylene glycol	to 1 ml

Note

The above formulations may be obtained by conventional procedures well known in the pharmaceutical art. The tablets (a)-(c) may be enteric coated by conventional means, for example to provide a coating of cellulose acetate phthalate. The aerosol formulations (h)-(k) may be used in conjunction with standard, metered dose aerosol dispensers, and the suspending agents sorbitan trioleate and soya lecithin may be replaced by an alternative suspending agent such as sorbitan monooleate, sorbitan sesquioleate, polysorbate 80, polyglycerol oleate or oleic acid.

CLAIMS

1. The use of a compound of the Formula I



Formula I

wherein:

R^1 and R^2, which may be the same or different are selected from hydroxy, C_{1-6}alkoxy, mercapto, C_{1-6}alkylthio, amino, C_{1-6}alkylamino, di-(C_{1-6}alkyl)amino, carboxy, C_{1-6}alkoxycarbonyl, carbamoyl, C_{1-6}alkylcarbamoyl, di-C_{1-6}alkylcarbamoyl, C_{1-6}alkylsulphonyl, arylsulphonyl, C_{1-6}alkylaminosulphonyl, di-(C_{1-6}alkyl)aminosulphonyl, nitro, cyano, cyanoC_{1-6}alkyl, hydroxyC_{1-6}alkyl, aminoC_{1-6}alkyl, C_{1-6}alkanoylamino, C_{1-6}alkoxycarbonylamino, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, C_{1-6}alkyl, halo, trifluoromethyl, aryl, arylC_{1-6}alkyl, arylC_{1-6}alkoxy, heteroaryl, heteroarylC_{1-6}alkyl, heterocyclyl and heterocyclylC_{1-6}alkyl;

m and p, are independently 0-3, and when m and/or p is 2 or 3 each R group may be the same or different;

R^3 is C_{1-4}alkyl;

q is 0-4;

R^4 is aryl or cycloalkyl wherein R^4 is optionally substituted with up to 3 substituents having any value defined for R^1;

or a pharmaceutically-acceptable salt or in vivo cleavable ester thereof in the manufacture of a medicament for use in the treatment of diseases or medical conditions mediated by cytokines.

2. A compound of the Formula I according to claim 1 for use in a method of treatment of the human or animal body by therapy except that

N-[5-(3-cyclohexylpropionamido)-2-methylphenyl]-4-hydroxybenzamide,

N-[5-(3-cyclohexylpropionamido)-2-methylphenyl]-4-acetoxybenzamide,

N-[5-(3-cyclohexylpropionamido)-2-methylphenyl]benzamide,
N-[5-(3-cyclohexylpropionamido)-2-methylphenyl]-3-hydroxybenzamide,
N-[5-(3-cyclohexylpropionamido)-2-methylphenyl]-2-hydroxybenzamide,
N-[5-(3-cyclohexylpropionamido)-2-methylphenyl]-4-methoxycarbonylbenzamide,
N-[5-(3-cyclohexylpropionamido)-2-methylphenyl]-4-hydroxymethylbenzamide,
N-[5-(3-cyclohexylpropionamido)-2-methylphenyl]-4-nitrobenzamide,
N-[5-(3-cyclohexylpropionamido)-2-methylphenyl]-4-aminobenzamide,
N-[5-(2-cyclohexylacetamido)-2-methylphenyl]-4-acetoxybenzamide,
N-[5-(4-cyclohexylbutyrylamino)-2-methylphenyl]-4-hydroxybenzamide,
N-[5-(3-cyclopentylpropionamido)-2-methylphenyl]-4-hydroxybenzamide,
N-[5-(3-phenylpropionamido)-2-methylphenyl]-4-hydroxybenzamide,
N-[5-(2-bicyclo[2.2.1]hept-2-ylacetamido)-2-methylphenyl]-4-hydroxybenzamide,
N-{5-[2-(3,4-dichlorophenyl)acetamido]-2-methylphenyl}-4-hydroxybenzamide,
N-[5-(3-dimethylaminobenzamido)-2-methylphenyl]-4-hydroxybenzamide,
N-[5-(4-cyclohexylbutyrylamino)-2-methylphenyl]-4-acetoxybenzamide,
N-[5-(3-phenylpropionamido)-2-methylphenyl]-4-acetoxybenzamide and
N-[5-(3-cyclopentylpropionamido)-2-methylphenyl]-4-acetoxybenzamide
are excluded.

3. A pharmaceutical composition which comprises an amide derivative of the Formula I, or a pharmaceutically-acceptable salt or in vivo cleavable ester thereof, according to claim 2 in association with a pharmaceutically-acceptable diluent or carrier.

4. An amide derivative of the Formula I according to claim 1 wherein R^1 is hydroxy, methoxy, ethoxy, propoxy, isopropoxy, butoxy, amino, methylamino, dimethylamino, carboxy, methoxycarbonyl, nitro, cyano, acetamido, acetyl, acetoxy, methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, fluoro, chloro, bromo, trifluoromethyl, pyrrolidin-1-yl, piperidino, morpholino, 4-thiamorpholino, piperazin-1-yl, 4-methylpiperazin-1-yl, 4-methylhomopiperazin-1-yl, pyrrolidin-1-ylmethyl, piperidinomethyl, 4-carbamoylpiperidin-1-ylmethyl, morpholinomethyl, 4-thiamorpholinomethyl, piperazin-1-ylmethyl, 4-methylpiperazin-1-ylmethyl, 4-ethylpiperazin-1-ylmethyl,

4-propylpiperazin-1-ylmethyl, 4-isopropylpiperazin-1-ylmethyl, 4-acetylpiperazin-1-ylmethyl and 4-methylhomopiperazin-1-ylmethyl;
m is 1, 2 or 3;
p is 0;
R^3 is methyl;
q is 0; and
R^4 is phenyl which is optionally substituted with 1 or 2 substituents selected from hydroxy, methoxy, ethoxy, amino, methylamino, dimethylamino, methoxycarbonyl, nitro, cyano, acetamido, fluoro, chloro, bromo, trifluoromethyl, phenyl, benzyloxy, pyrrolidin-1-yl, piperidino, morpholino, 4-thiamorpholino, piperazin-1-yl, 4-methylpiperazin-1-yl, 4-methylhomopiperazin-1-yl, pyrrolidin-1-ylmethyl, piperidinomethyl, 4-carbamoylpiperidin-1-ylmethyl, morpholinomethyl, 4-thiamorpholinomethyl, piperazin-1-ylmethyl, 4-methylpiperazin-1-ylmethyl, 4-ethylpiperazin-1-ylmethyl, 4-propylpiperazin-1-ylmethyl, 4-isopropylpiperazin-1-ylmethyl, 4-acetylpiperazin-1-ylmethyl and 4-methylhomopiperazin-1-ylmethyl;
or a pharmaceutically-acceptable salt thereof;
except that N-[5-(3-dimethylaminobenzamido)-2-methylphenyl]-4-hydroxybenzamide, N-[5-(2-hydroxybenzamido)-2-methylphenyl]-2-hydroxybenzamide, N-[5-(4-methoxybenzamido)-2-methylphenyl]-4-methoxybenzamide, N-[5-(3-methoxycarbonylbenzamido)-2-methylphenyl]-3-methoxycarbonylbenzamide and N-[5-(4-methoxycarbonylbenzamido)-2-methylphenyl]-4-methoxycarbonylbenzamide are excluded.

5. An amide derivative of the Formula I according to claim 1 wherein R^1 is hydroxy, methoxy, ethoxy, propoxy, isopropoxy, butoxy, amino, methylamino, dimethylamino, carboxy, methoxycarbonyl, nitro, cyano, acetamido, acetyl, acetoxy, methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, fluoro, chloro, bromo, trifluoromethyl, pyrrolidin-1-yl, piperidino, morpholino, 4-thiamorpholino, piperazin-1-yl, 4-methylpiperazin-1-yl, 4-methylhomopiperazin-1-yl, pyrrolidin-1-ylmethyl, piperidinomethyl, 4-carbamoylpiperidin-1-ylmethyl, morpholinomethyl, 4-thiamorpholinomethyl, piperazin-1-ylmethyl, 4-methylpiperazin-1-ylmethyl,

4-ethylpiperazin-1-ylmethyl, 4-propylpiperazin-1-ylmethyl, 4-isopropylpiperazin-1-ylmethyl, 4-acetylpiperazin-1-ylmethyl and 4-methylhomopiperazin-1-ylmethyl;

m is 1, 2 or 3;

p is 0;

R^3 is methyl;

q is 1, 2, 3 or 4; and

R^4 is cyclopentyl or cyclohexyl;

or a pharmaceutically-acceptable salt thereof;

except that N-[5-(3-cyclohexylpropionamido)-2-methylphenyl]-4-hydroxybenzamide, N-[5-(3-cyclohexylpropionamido)-2-methylphenyl]-4-acetoxybenzamide, N-[5-(3-cyclohexylpropionamido)-2-methylphenyl]-3-hydroxybenzamide, N-[5-(3-cyclohexylpropionamido)-2-methylphenyl]-2-hydroxybenzamide, N-[5-(3-cyclohexylpropionamido)-2-methylphenyl]-4-methoxycarbonylbenzamide, N-[5-(3-cyclohexylpropionamido)-2-methylphenyl]-4-nitrobenzamide, N-[5-(3-cyclohexylpropionamido)-2-methylphenyl]-4-aminobenzamide, N-[5-(2-cyclohexylacetamido)-2-methylphenyl]-4-acetoxybenzamide, N-[5-(4-cyclohexylbutyrylamino)-2-methylphenyl]-4-hydroxybenzamide, N-[5-(3-cyclopentylpropionamido)-2-methylphenyl]-4-hydroxybenzamide, N-[5-(4-cyclohexylbutyrylamino)-2-methylphenyl]-4-acetoxybenzamide and N-[5-(3-cyclopentylpropionamido)-2-methylphenyl]-4-acetoxybenzamide are excluded.

6. An amide derivative of the Formula I according to claim 1 wherein R^1 is hydroxy, methoxy, ethoxy, propoxy, isopropoxy, butoxy, carboxy, methoxycarbonyl, nitro, cyano, acetamido, acetyl, methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, fluoro, chloro, bromo or trifluoromethyl;

m is 0-3 and when m is 2 or 3 each R^1 group is the same or different;

p is 0;

R^3 is methyl;

q is 0; and

R^4 is phenyl which is substituted at the 3- or 4-position with a substituent selected from amino, methylamino, dimethylamino, aminomethyl, pyrrolidin-1-yl, piperidino, morpholino, 4-thiamorpholino, piperazin-1-yl, 4-methylpiperazin-1-yl, 4-methylhomopiperazin-1-yl, pyrrolidin-1-ylmethyl, piperidinomethyl, 4-carbamoylpiperidin-1-ylmethyl, morpholinomethyl, 4-thiamorpholinomethyl, piperazin-1-ylmethyl, 4-methylpiperazin-1-ylmethyl, 4-ethylpiperazin-1-ylmethyl, 4-propylpiperazin-1-ylmethyl, 4-isopropylpiperazin-1-ylmethyl, 4-acetylpiperazin-1-ylmethyl and 4-methylhomopiperazin-1-ylmethyl;

or a pharmaceutically-acceptable salt thereof;

except that N-[5-(3-dimethylaminobenzamido)-2-methylphenyl]-4-hydroxybenzamide is excluded.

7. An amide derivative of the Formula I according to claim 1

wherein R^1 is amino, methylamino, dimethylamino, aminomethyl, pyrrolidin-1-yl, piperidino, morpholino, 4-thiamorpholino, piperazin-1-yl, 4-methylpiperazin-1-yl, 4-methylhomopiperazin-1-yl, pyrrolidin-1-ylmethyl, piperidinomethyl, 4-carbamoylpiperidin-1-ylmethyl, morpholinomethyl, 4-thiamorpholinomethyl, piperazin-1-ylmethyl, 4-methylpiperazin-1-ylmethyl, 4-ethylpiperazin-1-ylmethyl, 4-propylpiperazin-1-ylmethyl, 4-isopropylpiperazin-1-ylmethyl, 4-acetylpiperazin-1-ylmethyl or 4-methylhomopiperazin-1-ylmethyl;

m is 1 with the R^1 group located at the 3- or 4-position;

p is 0;

R^3 is methyl;

q is 0; and

R^4 is phenyl which is optionally substituted with 1 or 2 substituents, which may be the same or different, selected from hydroxy, methoxy, ethoxy, carboxy, methoxycarbonyl, cyano, methyl, fluoro, chloro and trifluoromethyl;

or a pharmaceutically-acceptable salt thereof.

8. An amide derivative of the Formula I according to claim 1

wherein R^1 is amino, methylamino, dimethylamino, aminomethyl, pyrrolidin-1-yl, piperidino,

morpholino, 4-thiamorpholino, piperazin-1-yl, 4-methylpiperazin-1-yl, 4-methylhomopiperazin-1-yl, pyrrolidin-1-ylmethyl, piperidinomethyl, 4-carbamoylpiperidin-1-ylmethyl, morpholinomethyl, 4-thiamorpholinomethyl, piperazin-1-ylmethyl, 4-methylpiperazin-1-ylmethyl, 4-ethylpiperazin-1-ylmethyl, 4-propylpiperazin-1-ylmethyl, 4-isopropylpiperazin-1-ylmethyl, 4-acetylpiperazin-1-ylmethyl or 4-methylhomopiperazin-1-ylmethyl;

m is 1 with the R^1 group located at the 3- or 4-position;

p is 0;

R^3 is methyl;

q is 0; and

R^4 is phenyl which is substituted at the 3- or 4-position with a substituent selected from amino, methylamino, dimethylamino, aminomethyl, pyrrolidin-1-yl, piperidino, morpholino, 4-thiamorpholino, piperazin-1-yl, 4-methylpiperazin-1-yl, 4-methylhomopiperazin-1-yl, pyrrolidin-1-ylmethyl, piperidinomethyl, 4-carbamoylpiperidin-1-ylmethyl, morpholinomethyl, 4-thiamorpholinomethyl, piperazin-1-ylmethyl, 4-methylpiperazin-1-ylmethyl, 4-ethylpiperazin-1-ylmethyl, 4-propylpiperazin-1-ylmethyl, 4-isopropylpiperazin-1-ylmethyl, 4-acetylpiperazin-1-ylmethyl and 4-methylhomopiperazin-1-ylmethyl;

or a pharmaceutically-acceptable salt thereof.

9. A compound of the Formula I according to claim 1 which is:-

N-[2-methyl-5-(3-morpholinobenzamido)phenyl]-3,4,5-trimethoxybenzamide,

and pharmaceutically-acceptable salts thereof.

10. A compound of the Formula I according to claim 1 selected from:-

N-(5-benzamido-2-methylphenyl)-3-(piperazin-1-yl)methylbenzamide,

N-(5-benzamido-2-methylphenyl)-3-(4-methylpiperazin-1-yl)methylbenzamide,

N-[2-methyl-5-(3-trifluoromethylbenzamido)phenyl]-3-(4-methylpiperazin-1-yl)methylbenzamide,

N-[5-(3-chlorobenzamido)-2-methylphenyl]-3-(4-methylpiperazin-1-yl)methylbenzamide,

N-[5-(2-methoxybenzamido)-2-methylphenyl]-3-(4-methylpiperazin-1-yl)methylbenzamide and N-[5-(3-ethoxybenzamido)-2-methylphenyl]-3-(4-methylpiperazin-1-yl)methylbenzamide;

and pharmaceutically-acceptable salts thereof.

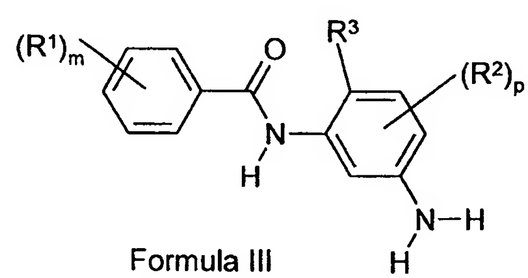
11. A compound of the Formula I according to claim 1 selected from:-

N-[2-methyl-5-(3-morpholinobenzamido)phenyl]-3-morpholinobenzamide and N-[2-methyl-5-(3-morpholinobenzamido)phenyl]-3-(4-methylpiperazin-1-yl)methylbenzamide;

and pharmaceutically-acceptable salts thereof.

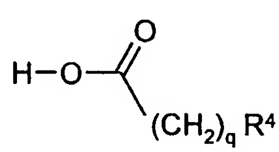
12. A process for the preparation of an amide derivative of the Formula I, or a pharmaceutically-acceptable salt or in vivo cleavable ester thereof, according to claim 1 which comprises:-

(a) the reaction of a compound of the Formula III



Formula III

with a compound of the Formula IV



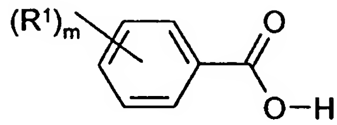
Formula IV

or an activated derivative thereof, under standard amide bond forming conditions, wherein variable groups are as defined in claim 1 and wherein any functional group is protected, if necessary, and:

i. removing any protecting groups;

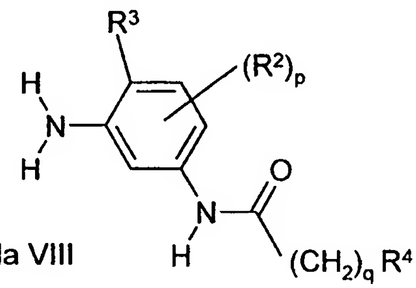
ii. optionally forming a pharmaceutically-acceptable salt or in vivo cleavable ester;

(b) the reaction of an acid of the Formula VI



Formula VI

or an activated derivative thereof, with an aniline of the Formula VIII



Formula VIII

under standard amide bond forming conditions, wherein variable groups are as defined in claim 1 and wherein any functional group is protected, if necessary, and:

i. removing any protecting groups;

ii. optionally forming a pharmaceutically-acceptable salt or <u>in vivo</u> cleavable ester;

(c) for the preparation of a compound of the Formula I according to claim 1 wherein R^1 or a substituent on R^4 is heterocyclylC_{1-6}alkyl, the reaction of a compound of the Formula I wherein R^1 or a substituent on R^4 is a group of the formula -C_{1-6}alkyl-Z wherein Z is a displaceable group with a heterocyclyl compound;

(d) for the preparation of a compound of the Formula I according to claim 1 wherein R^1, R^2 or a substituent on R^4 is carboxy, the cleavage of a compound of the Formula I wherein R^1, R^2 or a substituent on R^4 is C_{1-6}alkoxycarbonyl;

(e) for the preparation of a compound of the Formula I according to claim 1 wherein R^1, R^2 or a substituent on R^4 is hydroxy, the cleavage of a compound of the Formula I wherein R^1, R^2 or a substituent on R^4 is benzyloxy or substituted benzyloxy;

(f) for the preparation of a compound of the Formula I according to claim 1 wherein R^1, R^2 or a substituent on R^4 is amino, the reduction of a compound of the Formula I wherein R^1, R^2 or a substituent on R^4 is nitro; or

(g) for the preparation of a compound of the Formula I according to claim 1 wherein R^1, R^2 or a substituent on R^4 is C_{1-6}alkanoylamino, the acylation of a compound of the Formula I wherein R^1, R^2 or a substituent on R^4 is amino.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 98/02826

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/165 C07C235/56

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DATABASE WPI Derwent Publications Ltd., London, GB; AN 323139 XP002086154 "new n-substituted cyclic carboxamide compounds are inflammatory cytokine inhibitors used as antiinflammatory agents" & JP 409 124 571 A (JAPAN TOBACCO INC) see abstract see examples: p. 56 and following ---	1-11
A	HANSON G.J.: "inhibitors of p38 kinase" EXPERT OPINION ON THERAPEUTIC PATENTS, vol. 7, no. 7, 1997, pages 729-733, XP002086152 cited in the application see the whole document ---	1-11
	-/--	

[X] Further documents are listed in the continuation of box C.

[ ] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 November 1998	14/12/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Trifilieff-Riolo, S

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/GB 98/02826

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: -
because they relate to subject matter not required to be searched by this Authority, namely:
See below

2. [X] Claims Nos.: -
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
In view of the large number of compounds which are defined by the wording "in vivo cleavable ester" in claim 1, the search has been performed on the compounds covered by formula I and the salts thereof.

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	ASHTON ET AL: "now low-density lipoprotein receptor upregulators acting via a novel mechanism" J. MED. CHEM., vol. 39, no. 17, 1996, pages 3343-3356, XP002086153 cited in the application see page 3344 - page 3346 -----	1-12

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9822483.5	16 October 1998 (16.10.98)	GB

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(72) Inventors; and

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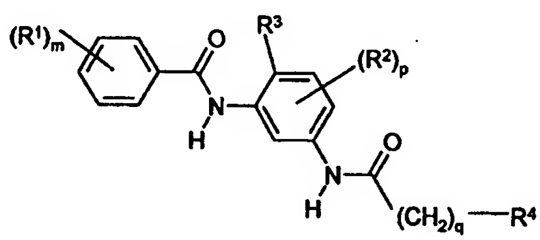
(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: BENZAMIDE DERIVATIVES FOR THE TREATMENT OF DISEASES MEDIATED BY CYTOKINES



(I)

(57) Abstract

The invention concerns amide derivatives of Formula (I), wherein R^3 is (1–6C)alkyl or halogeno; m is 1–3 and R^1 is selected from substituents such as: (A) hydroxy, halogeno, (1–6C)alkyl, (1–6C)alkoxy, aryl, heteroaryl and heterocyclyl; and (B) di–[(1–6C)alkyl]amino–(1–6C)alkyl, (1–6C)alkoxy–(2–6C)alkoxy, di–[(1–6C)alkyl]amino–(2–6C)alkoxy, aryloxy, heteroaryloxy, heteroaryl–(1–6C)alkoxy, heterocyclyloxy and heterocyclyl–(1–6C)alkoxy; p is 0–2 and R^2 is a substituent such as hydroxy and halogeno; q is 0–4; and R^4 is aryl or cycloalkyl which bears 1–3 substituents such as: (C) hydrogen, hydroxy, halogeno and heterocyclyl; and (D) heteroaryl–(1–6C)alkoxy and heterocyclyl–(1–6C)alkoxy, provided that a sustituent on R^4 is selected from paragraph (C) only if at least one R^1 group is selected from paragraph (B); processes for their preparation, pharmaceutical compositions containing them and their use in the treatment of diseases or medical conditions mediated by cytokines.

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BENZAMIDE DERIVATIVES FOR THE TREATMENT OF DISEASES MEDIATED BY CYTOKINES

This invention concerns certain amide derivatives which are useful as inhibitors of cytokine mediated disease. The invention also concerns processes for the manufacture of the amide derivatives of the invention, pharmaceutical compositions containing them and their use in therapeutic methods, for example by virtue of inhibition of cytokine mediated disease.

The amide derivatives disclosed in the present invention are inhibitors of the production of cytokines such as Tumour Necrosis Factor (hereinafter TNF), for example TNFα, and various members of the interleukin (hereinafter IL) family, for example IL-1, IL-6 and IL-8. Accordingly the compounds of the invention will be useful in the treatment of diseases or medical conditions in which excessive production of cytokines occurs, for example excessive production of TNFα or IL-1. It is known that cytokines are produced by a wide variety of cells such as monocytes and macrophages and that they give rise to a variety of physiological effects which are believed to be important in disease or medical conditions such as inflammation and immunoregulation. For example, TNFα and IL-1 have been implicated in the cell signalling cascade which is believed to contribute to the pathology of disease states such as inflammatory and allergic diseases and cytokine-induced toxicity. It is also known that, in certain cellular systems, TNFα production precedes and mediates the production of other cytokines such as IL-1.

Abnormal levels of cytokines have also been implicated in, for example, the production of physiologically-active eicosanoids such as the prostaglandins and leukotrienes, the stimulation of the release of proteolytic enzymes such as collagenase, the activation of the immune system, for example by stimulation of T-helper cells, the activation of osteoclast activity leading to the resorption of calcium, the stimulation of the release of proteoglycans from, for example, cartilage, the stimulation of cell proliferation and to angiogenesis.

Cytokines are also believed to be implicated in the production and development of disease states such as inflammatory and allergic diseases, for example inflammation of the joints (especially rheumatoid arthritis, osteoarthritis and gout), inflammation of the gastrointestinal tract (especially inflammatory bowel disease, ulcerative colitis, Crohn's disease and gastritis), skin disease (especially psoriasis, eczema and dermatitis) and respiratory disease (especially asthma, bronchitis, allergic rhinitis and adult respiratory

distress syndrome), and in the production and development of various cardiovascular and cerebrovascular disorders such as congestive heart failure, myocardial infarction, the formation of atherosclerotic plaques, hypertension, platelet aggregation, angina, stroke, reperfusion injury, vascular injury including restenosis and peripheral vascular disease, and, for example, various disorders of bone metabolism such as osteoporosis (including senile and postmenopausal osteoporosis), Paget's disease, bone metastases, hypercalcaemia, hyperparathyroidism, osteosclerosis, osteoperosis and periodontitis, and the abnormal changes in bone metabolism which may accompany rheumatoid arthritis and osteoarthritis. Excessive cytokine production has also been implicated in mediating certain complications of bacterial, fungal and/or viral infections such as endotoxic shock, septic shock and toxic shock syndrome and in mediating certain complications of CNS surgery or injury such as neurotrauma and ischaemic stroke. Excessive cytokine production has also been implicated in mediating or exacerbating the development of diseases involving cartilage or muscle resorption, pulmonary fibrosis, cirrhosis, renal fibrosis, the cachexia found in certain chronic diseases such as malignant disease and acquired immune deficiency syndrome (AIDS), tumour invasiveness and tumour metastasis and multiple sclerosis.

Evidence of the central role played by TNFα in the cell signalling cascade which gives rise to rheumatoid arthritis is provided by the efficacy in clinical studies of antibodies of TNFα (The Lancet, 1994, 344, 1125 and British Journal of Rheumatology, 1995, 34, 334).

Thus cytokines such as TNFα and IL-1 are believed to be important mediators of a considerable range of diseases and medical conditions. Accordingly it is expected that inhibition of the production of and/or effects of these cytokines will be of benefit in the prophylaxis, control or treatment of such diseases and medical conditions.

Without wishing to imply that the compounds disclosed in the present invention possess pharmacological activity only by virtue of an effect on a single biological process, it is believed that the compounds inhibit the effects of cytokines by virtue of inhibition of the enzyme p38 kinase. p38 kinase, otherwise known as cytokine suppressive binding protein (hereinafter CSBP) and reactivating kinase (hereinafter RK), is a member of the mitogen-activated protein (hereinafter MAP) kinase family of enzymes which is known to be activated by physiological stress such as that induced by ionising radiation, cytotoxic agents, and toxins, for example endotoxins such as bacterial lipopolysaccharide, and by a variety of agents

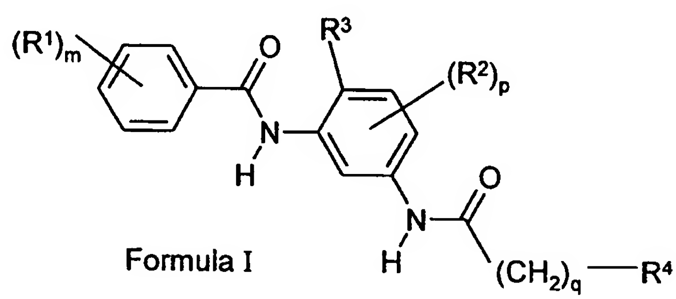
such as the cytokines, for example TNFα and IL-1. It is known that p38 kinase phosphorylates certain intracellular proteins which are involved in the cascade of enzymatic steps which leads to the biosynthesis and excretion of cytokines such as TNFα and IL-1. Known inhibitors of p38 kinase have been reviewed by G. J. Hanson in Expert Opinions on Therapeutic Patents, 1997, 7, 729-733. p38 kinase is known to exist in isoforms identified as p38α and p38β.

The compounds disclosed in the present invention are inhibitors of the production of cytokines such as TNF, in particular of TNFα, and various interleukins, in particular IL-1.

It is known from J. Med. Chem., 1996, 39, 3343-3356, that certain benzamide derivatives can upregulate the expression of the low density lipoprotein (LDL) receptor in human hepatocyte cells. The disclosed compounds included certain N-(2-methylphenyl)-, N-(2-methoxyphenyl)- and N-(2-halogenophenyl)-benzamide derivatives. One of the disclosed compounds is N-[5-(3-cyclohexylpropionamido)-2-methylphenyl]-3,4-methylenedioxybenzamide.

It is known from US Patent No. 4,367,328 (Chemical Abstracts, 98, 144515) that certain epoxy resins may be prepared from the chemical intermediate N-{5-[2-(2,3-epoxypropoxy)benzamido]-2-methylphenyl}-2-(2,3-epoxypropoxy)benzamide.

According to one aspect of the present invention there is provided a compound of the Formula I



Formula I

wherein R^3 is (1-6C)alkyl or halogeno;

R^1 is selected from the substituents defined in paragraphs (A) and (B) hereinafter:-

(A) hydroxy, halogeno, trifluoromethyl, cyano, mercapto, nitro, amino, carboxy, carbamoyl, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl,

(1-6C)alkanoyl, cyano-(1-6C)alkyl, hydroxy-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkanoyloxy, (1-6C)alkanoylamino, (1-6C)alkoxycarbonylamino, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, aryl, aryl-(1-6C)alkyl, aryl-(1-6C)alkoxy, arylthio, arylsulphinyl, arylsulphonyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl and heterocyclyl-(1-6C)alkyl; and

(B) (1-3C)alkylenedioxy, halogeno-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, carboxy-(1-6C)alkyl, (1-6C)alkoxycarbonyl-(1-6C)alkyl, carbamoyl-(1-6C)alkyl, N-(1-6C)alkylcarbamoyl-(1-6C)alkyl, N,N-di-[(1-6C)alkyl]carbamoyl-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl, hydroxy-(2-6C)alkoxy-(1-6C)alkyl, (1-6C)alkoxy-(2-6C)alkoxy-(1-6C)alkyl, hydroxy-(2-6C)alkylamino-(1-6C)alkyl, (1-6C)alkoxy-(2-6C)alkylamino-(1-6C)alkyl, amino-(2-6C)alkylamino-(1-6C)alkyl, (1-6C)alkylamino-(2-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(2-6C)alkylamino-(1-6C)alkyl, (1-6C)alkylthio-(1-6C)alkyl, hydroxy-(2-6C)alkylthio-(1-6C)alkyl, (1-6C)alkoxy-(2-6C)alkylthio-(1-6C)alkyl, hydroxy-N-(1-6C)alkyl-(2-6C)alkylamino-(1-6C)alkyl, (1-6C)alkoxy-N-(1-6C)alkyl-(2-6C)alkylamino-(1-6C)alkyl, amino-N-(1-6C)alkyl-(2-6C)alkylamino-(1-6C)alkyl, (1-6C)alkylamino-N-(1-6C)alkyl-(2-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-N-(1-6C)alkyl-(2-6C)alkylamino-(1-6C)alkyl, trifluoromethoxy, halogeno-(2-6C)alkoxy, hydroxy-(2-6C)alkoxy, (1-6C)alkoxy-(2-6C)alkoxy, cyano-(1-6C)alkoxy, carboxy-(1-6C)alkoxy, (1-6C)alkoxycarbonyl-(1-6C)alkoxy, carbamoyl-(1-6C)alkoxy, N-(1-6C)alkylcarbamoyl-(1-6C)alkoxy, N,N-di-[(1-6C)alkyl]carbamoyl-(1-6C)alkoxy, amino-(2-6C)alkoxy, (1-6C)alkylamino-(2-6C)alkoxy, di-[(1-6C)alkyl]amino-(2-6C)alkoxy, halogeno-(2-6C)alkylamino, hydroxy-(2-6C)alkylamino, (1-6C)alkoxy-(2-6C)alkylamino, cyano-(1-6C)alkylamino, carboxy-(1-6C)alkylamino, (1-6C)alkoxycarbonyl-(1-6C)alkylamino, carbamoyl-(1-6C)alkylamino, N-(1-6C)alkylcarbamoyl-(1-6C)alkylamino, N,N-di-[(1-6C)alkyl]carbamoyl-(1-6C)alkylamino, amino-(2-6C)alkylamino, (1-6C)alkylamino-(2-6C)alkylamino, di-[(1-6C)alkyl]amino-(2-6C)alkylamino, N-(1-6C)alkyl-halogeno-(1-6C)alkylamino, N-(1-6C)alkyl-hydroxy-(2-6C)alkylamino, N-(1-6C)alkyl-(1-6C)alkoxy-(2-6C)alkylamino, N-(1-6C)alkyl-cyano-(1-6C)alkylamino, N-(1-6C)alkyl-carboxy-(1-6C)alkylamino, N-(1-6C)alkyl-(1-6C)alkoxycarbonyl-(1-6C)alkylamino, N-(1-6C)alkyl-carbamoyl-(1-6C)alkylamino, N-(1-6C)alkyl-

N-(1-6C)alkylcarbamoyl-(1-6C)alkylamino, N-(1-6C)alkyl-N,N-di-[(1-6C)alkyl]carbamoyl-(1-6C)alkylamino, N-(1-6C)alkyl-amino-(2-6C)alkylamino, N-(1-6C)alkyl-(1-6C)alkylamino-(2-6C)alkylamino, N-(1-6C)alkyl-di-[(1-6C)alkyl]amino-(2-6C)alkylamino, (1-6C)alkanesulphonylamino, N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, halogeno-(2-6C)alkanoylamino, hydroxy-(2-6C)alkanoylamino, (1-6C)alkoxy-(2-6C)alkanoylamino, cyano-(2-6C)alkanoylamino, carboxy-(2-6C)alkanoylamino, (1-6C)alkoxycarbonyl-(2-6C)alkanoylamino, carbamoyl-(2-6C)alkanoylamino, N-(1-6C)alkylcarbamoyl-(2-6C)alkanoylamino, N,N-di-[(1-6C)alkyl]carbamoyl-(2-6C)alkanoylamino, amino-(2-6C)alkanoylamino, (1-6C)alkylamino-(2-6C)alkanoylamino, di-[(1-6C)alkyl]amino-(2-6C)alkanoylamino, aryloxy, arylamino, aryl-(1-6C)alkylamino, N-(1-6C)alkyl-aryl-(1-6C)alkylamino, aroylamino, arylsulphonylamino, N-arylsulphamoyl, aryl-(2-6C)alkanoylamino, aryl-(1-6C)alkoxy-(1-6C)alkyl, aryl-(1-6C)alkylamino-(1-6C)alkyl, N-(1-6C)alkyl-aryl-(1-6C)alkylamino-(1-6C)alkyl, heteroaryloxy, heteroaryl-(1-6C)alkoxy, heteroarylamino, heteroaryl-(1-6C)alkylamino, N-(1-6C)alkyl-heteroaryl-(1-6C)alkylamino, heteroarylcarbonylamino, heteroarylsulphonylamino, N-heteroarylsulphamoyl, heteroaryl-(2-6C)alkanoylamino, heteroaryl-(1-6C)alkoxy-(1-6C)alkyl, heteroaryl-(1-6C)alkylamino-(1-6C)alkyl, N-(1-6C)alkyl-heteroaryl-(1-6C)alkylamino-(1-6C)alkyl, heterocyclyloxy, heterocyclyl-(1-6C)alkoxy, heterocyclylamino, heterocyclyl-(1-6C)alkylamino, N-(1-6C)alkyl-heterocyclyl-(1-6C)alkylamino, heterocyclylcarbonylamino, heterocyclylsulphonylamino, N-heterocyclylsulphamoyl, heterocyclyl-(2-6C)alkanoylamino, heterocyclyl-(1-6C)alkoxy-(1-6C)alkyl, heterocyclyl-(1-6C)alkylamino-(1-6C)alkyl and N-(1-6C)alkyl-heterocyclyl-(1-6C)alkylamino-(1-6C)alkyl;

and wherein any aryl, heteroaryl or heterocyclyl group in a R^1 substituent may optionally bear 1 or 2 substituents selected from halogeno, (1-6C)alkyl and (1-6C)alkoxy;

and wherein any of the substituents defined in paragraph (B) hereinbefore which comprise a CH_2 group which is attached to 2 carbon atoms or a CH_3 group which is attached to a carbon atom may optionally bear on each said CH_2 or CH_3 group a substituent selected from hydroxy, amino, (1-6C)alkoxy, (1-6C)alkylamino and di-[(1-6C)alkyl]amino;

m is 1, 2 or 3;

R^2 is hydroxy, halogeno, trifluoromethyl, cyano, mercapto, nitro, amino, carboxy,

(1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkoxy, (1-6C)alkylamino or di-[(1-6C)alkyl]amino;

p is 0, 1 or 2;

q is 0, 1, 2, 3 or 4; and

R^4 is aryl or cycloalkyl wherein R^4 is substituted with 1, 2 or 3 substituents selected from paragraphs (C) and (D) hereinafter:

(C) hydrogen, hydroxy, halogeno, trifluoromethyl, cyano, mercapto, nitro, amino, carboxy, carbamoyl, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (1-6C)alkanoyl, cyano-(1-6C)alkyl, hydroxy-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkanoyloxy, (1-6C)alkanoylamino, (1-6C)alkoxycarbonylamino, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, aryl, aryl-(1-6C)alkyl, aryl-(1-6C)alkoxy, arylthio, arylsulphinyl, arylsulphonyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl and heterocyclyl-(1-6C)alkyl; and

(D) (1-3C)alkylenedioxy, halogeno-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, carboxy-(1-6C)alkyl, (1-6C)alkoxycarbonyl-(1-6C)alkyl, carbamoyl-(1-6C)alkyl, N-(1-6C)alkylcarbamoyl-(1-6C)alkyl, N,N-di-[(1-6C)alkyl]carbamoyl-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl, hydroxy-(2-6C)alkoxy-(1-6C)alkyl, (1-6C)alkoxy-(2-6C)alkoxy-(1-6C)alkyl, hydroxy-(2-6C)alkylamino-(1-6C)alkyl, (1-6C)alkoxy-(2-6C)alkylamino-(1-6C)alkyl, amino-(2-6C)alkylamino-(1-6C)alkyl, (1-6C)alkylamino-(2-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(2-6C)alkylamino-(1-6C)alkyl, (1-6C)alkylthio-(1-6C)alkyl, hydroxy-(2-6C)alkylthio-(1-6C)alkyl, (1-6C)alkoxy-(2-6C)alkylthio-(1-6C)alkyl, hydroxy-N-(1-6C)alkyl-(2-6C)alkylamino-(1-6C)alkyl, (1-6C)alkoxy-N-(1-6C)alkyl-(2-6C)alkylamino-(1-6C)alkyl, amino-N-(1-6C)alkyl-(2-6C)alkylamino-(1-6C)alkyl, (1-6C)alkylamino-N-(1-6C)alkyl-(2-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-N-(1-6C)alkyl-(2-6C)alkylamino-(1-6C)alkyl, trifluoromethoxy, halogeno-(2-6C)alkoxy, hydroxy-(2-6C)alkoxy, (1-6C)alkoxy-(2-6C)alkoxy, cyano-(1-6C)alkoxy, carboxy-(1-6C)alkoxy, (1-6C)alkoxycarbonyl-(1-6C)alkoxy, carbamoyl-(1-6C)alkoxy, N-(1-6C)alkylcarbamoyl-(1-6C)alkoxy, N,N-di-[(1-6C)alkyl]carbamoyl-(1-6C)alkoxy, amino-(2-6C)alkoxy,

(1-6C)alkylamino-(2-6C)alkoxy, di-[(1-6C)alkyl]amino-(2-6C)alkoxy, halogeno-(2-6C)alkylamino, hydroxy-(2-6C)alkylamino, (1-6C)alkoxy-(2-6C)alkylamino, cyano-(1-6C)alkylamino, carboxy-(1-6C)alkylamino, (1-6C)alkoxycarbonyl-(1-6C)alkylamino, carbamoyl-(1-6C)alkylamino, N-(1-6C)alkylcarbamoyl-(1-6C)alkylamino, N,N-di-[(1-6C)alkyl]carbamoyl-(1-6C)alkylamino, amino-(2-6C)alkylamino, (1-6C)alkylamino-(2-6C)alkylamino, di-[(1-6C)alkyl]amino-(2-6C)alkylamino, N-(1-6C)alkyl-halogeno-(1-6C)alkylamino, N-(1-6C)alkyl-hydroxy-(2-6C)alkylamino, N-(1-6C)alkyl-(1-6C)alkoxy-(2-6C)alkylamino, N-(1-6C)alkyl-cyano-(1-6C)alkylamino, N-(1-6C)alkyl-carboxy-(1-6C)alkylamino, N-(1-6C)alkyl-(1-6C)alkoxycarbonyl-(1-6C)alkylamino, N-(1-6C)alkyl-carbamoyl-(1-6C)alkylamino, N-(1-6C)alkyl-N-(1-6C)alkylcarbamoyl-(1-6C)alkylamino, N-(1-6C)alkyl-N,N-di-[(1-6C)alkyl]carbamoyl-(1-6C)alkylamino, N-(1-6C)alkyl-amino-(2-6C)alkylamino, N-(1-6C)alkyl-(1-6C)alkylamino-(2-6C)alkylamino, N-(1-6C)alkyl-di-[(1-6C)alkyl]amino-(2-6C)alkylamino, (1-6C)alkanesulphonylamino, N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, halogeno-(2-6C)alkanoylamino, hydroxy-(2-6C)alkanoylamino, (1-6C)alkoxy-(2-6C)alkanoylamino, cyano-(2-6C)alkanoylamino, carboxy-(2-6C)alkanoylamino, (1-6C)alkoxycarbonyl-(2-6C)alkanoylamino, carbamoyl-(2-6C)alkanoylamino, N-(1-6C)alkylcarbamoyl-(2-6C)alkanoylamino, N,N-di-[(1-6C)alkyl]carbamoyl-(2-6C)alkanoylamino, amino-(2-6C)alkanoylamino, (1-6C)alkylamino-(2-6C)alkanoylamino, di-[(1-6C)alkyl]amino-(2-6C)alkanoylamino, aryloxy, arylamino, aryl-(1-6C)alkylamino, N-(1-6C)alkyl-aryl-(1-6C)alkylamino, aroylamino, arylsulphonylamino, N-arylsulphamoyl, aryl-(2-6C)alkanoylamino, aryl-(1-6C)alkoxy-(1-6C)alkyl, aryl-(1-6C)alkylamino-(1-6C)alkyl, N-(1-6C)alkyl-aryl-(1-6C)alkylamino-(1-6C)alkyl, heteroaryloxy, heteroaryl-(1-6C)alkoxy, heteroarylamino, heteroaryl-(1-6C)alkylamino, N-(1-6C)alkyl-heteroaryl-(1-6C)alkylamino, heteroarylcarbonylamino, heteroarylsulphonylamino, N-heteroarylsulphamoyl, heteroaryl-(2-6C)alkanoylamino, heteroaryl-(1-6C)alkoxy-(1-6C)alkyl, heteroaryl-(1-6C)alkylamino-(1-6C)alkyl, N-(1-6C)alkyl-heteroaryl-(1-6C)alkylamino-(1-6C)alkyl, heterocyclyloxy, heterocyclyl-(1-6C)alkoxy, heterocyclylamino, heterocyclyl-(1-6C)alkylamino, N-(1-6C)alkyl-heterocyclyl-(1-6C)alkylamino, heterocyclylcarbonylamino, heterocyclylsulphonylamino, N-heterocyclylsulphamoyl, heterocyclyl-(2-6C)alkanoylamino, heterocyclyl-(1-6C)alkoxy-

(1-6C)alkyl, heterocyclyl-(1-6C)alkylamino-(1-6C)alkyl and N-(1-6C)alkyl-heterocyclyl-(1-6C)alkylamino-(1-6C)alkyl;
and wherein any aryl, heteroaryl or heterocyclyl group in a substituent on R^4 may optionally bear 1 or 2 substituents selected from halogeno, (1-6C)alkyl and (1-6C)alkoxy;
and wherein any of the substituents defined in paragraph (D) hereinbefore which comprise a CH_2 group which is attached to 2 carbon atoms or a CH_3 group which is attached to a carbon atom may optionally bear on each said CH_2 or CH_3 group a substituent selected from hydroxy, amino, (1-6C)alkoxy, (1-6C)alkylamino and di-[(1-6C)alkyl]amino;
or a pharmaceutically-acceptable salt or in-vivo-cleavable ester thereof;
provided that a substituent on R^4 is selected from paragraph (C) hereinbefore only if at least one R^1 group is selected from paragraph (B) hereinbefore;
and provided that the compounds N-[5-(3-cyclohexylpropionamido)-2-methylphenyl]-3,4-methylenedioxybenzamide and N-{5-[2-(2,3-epoxypropoxy)benzamido]-2-methylphenyl}-2-(2,3-epoxypropoxy)benzamide are excluded.

According to a further aspect of the invention there is provided a compound of the Formula I
wherein R^3 is (1-6C)alkyl or halogeno;
R^1 is selected from the substituents defined in paragraphs (A) and (B) hereinafter:-

(A) hydroxy, halogeno, trifluoromethyl, cyano, mercapto, nitro, amino, carboxy, carbamoyl, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (1-6C)alkanoyl, cyano-(1-6C)alkyl, hydroxy-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkanoyloxy, (1-6C)alkanoylamino, (1-6C)alkoxycarbonylamino, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, aryl, aryl-(1-6C)alkyl, aryl-(1-6C)alkoxy, arylthio, arylsulphinyl, arylsulphonyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl and heterocyclyl-(1-6C)alkyl; and

(B) (1-3C)alkylenedioxy, halogeno-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, carboxy-(1-6C)alkyl, (1-6C)alkoxycarbonyl-(1-6C)alkyl, carbamoyl-(1-6C)alkyl, N-(1-6C)alkylcarbamoyl-(1-6C)alkyl, N,N-di-[(1-6C)alkyl]carbamoyl-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl, hydroxy-(2-6C)alkoxy-

(1-6C)alkyl, (1-6C)alkoxy-(2-6C)alkoxy-(1-6C)alkyl, hydroxy-(2-6C)alkylamino-(1-6C)alkyl, (1-6C)alkoxy-(2-6C)alkylamino-(1-6C)alkyl, amino-(2-6C)alkylamino-(1-6C)alkyl, (1-6C)alkylamino-(2-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(2-6C)alkylamino-(1-6C)alkyl, (1-6C)alkylthio-(1-6C)alkyl, hydroxy-(2-6C)alkylthio-(1-6C)alkyl, (1-6C)alkoxy-(2-6C)alkylthio-(1-6C)alkyl, halogeno-(2-6C)alkoxy, hydroxy-(2-6C)alkoxy, (1-6C)alkoxy-(2-6C)alkoxy, cyano-(1-6C)alkoxy, carboxy-(1-6C)alkoxy, (1-6C)alkoxycarbonyl-(1-6C)alkoxy, carbamoyl-(1-6C)alkoxy, N-(1-6C)alkylcarbamoyl-(1-6C)alkoxy, N,N-di-[(1-6C)alkyl]carbamoyl-(1-6C)alkoxy, amino-(2-6C)alkoxy, (1-6C)alkylamino-(2-6C)alkoxy, di-[(1-6C)alkyl]amino-(2-6C)alkoxy, halogeno-(2-6C)alkylamino, hydroxy-(2-6C)alkylamino, (1-6C)alkoxy-(2-6C)alkylamino, cyano-(1-6C)alkylamino, carboxy-(1-6C)alkylamino, (1-6C)alkoxycarbonyl-(1-6C)alkylamino, carbamoyl-(1-6C)alkylamino, N-(1-6C)alkylcarbamoyl-(1-6C)alkylamino, N,N-di-[(1-6C)alkyl]carbamoyl-(1-6C)alkylamino, amino-(2-6C)alkylamino, (1-6C)alkylamino-(2-6C)alkylamino, di-[(1-6C)alkyl]amino-(2-6C)alkylamino, N-(1-6C)alkyl-halogeno-(1-6C)alkylamino, N-(1-6C)alkyl-hydroxy-(2-6C)alkylamino, N-(1-6C)alkyl-(1-6C)alkoxy-(2-6C)alkylamino, N-(1-6C)alkyl-cyano-(1-6C)alkylamino, N-(1-6C)alkyl-carboxy-(1-6C)alkylamino, N-(1-6C)alkyl-(1-6C)alkoxycarbonyl-(1-6C)alkylamino, N-(1-6C)alkyl-carbamoyl-(1-6C)alkylamino, N-(1-6C)alkyl-N-(1-6C)alkylcarbamoyl-(1-6C)alkylamino, N-(1-6C)alkyl-N,N-di-[(1-6C)alkyl]carbamoyl-(1-6C)alkylamino, N-(1-6C)alkyl-amino-(2-6C)alkylamino, N-(1-6C)alkyl-(1-6C)alkylamino-(2-6C)alkylamino, N-(1-6C)alkyl-di-[(1-6C)alkyl]amino-(2-6C)alkylamino, (1-6C)alkanesulphonylamino, halogeno-(2-6C)alkanoylamino, hydroxy-(2-6C)alkanoylamino, (1-6C)alkoxy-(2-6C)alkanoylamino, cyano-(2-6C)alkanoylamino, carboxy-(2-6C)alkanoylamino, (1-6C)alkoxycarbonyl-(2-6C)alkanoylamino, carbamoyl-(2-6C)alkanoylamino, N-(1-6C)alkylcarbamoyl-(2-6C)alkanoylamino, N,N-di-[(1-6C)alkyl]carbamoyl-(2-6C)alkanoylamino, amino-(2-6C)alkanoylamino, (1-6C)alkylamino-(2-6C)alkanoylamino, di-[(1-6C)alkyl]amino-(2-6C)alkanoylamino, aryloxy, arylamino, aryl-(1-6C)alkylamino, N-(1-6C)alkyl-aryl-(1-6C)alkylamino, aroylamino, arylsulphonylamino, N-arylsulphamoyl, aryl-(2-6C)alkanoylamino, heteroaryloxy, heteroaryl-(1-6C)alkoxy, heteroarylamino, heteroaryl-(1-6C)alkylamino, N-(1-6C)alkyl-heteroaryl-(1-6C)alkylamino, heteroarylcarbonylamino,

heteroarylsulphonylamino, N-heteroarylsulphamoyl, heteroaryl-(2-6C)alkanoylamino, heterocyclyloxy, heterocyclyl-(1-6C)alkoxy, heterocyclylamino, heterocyclyl-(1-6C)alkylamino, N-(1-6C)alkyl-heterocyclyl-(1-6C)alkylamino, heterocyclylcarbonylamino, heterocyclylsulphonylamino, N-heterocyclylsulphamoyl and heterocyclyl-(2-6C)alkanoylamino, and wherein any aryl, heteroaryl or heterocyclyl group in a R^1 substituent may optionally bear 1 or 2 substituents selected from halogeno, (1-6C)alkyl and (1-6C)alkoxy;

m is 1, 2 or 3;

R^2 is hydroxy, halogeno, trifluoromethyl, cyano, mercapto, nitro, amino, carboxy, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkoxy, (1-6C)alkylamino or di-[(1-6C)alkyl]amino;

p is 0, 1 or 2;

q is 0, 1, 2, 3 or 4; and

R^4 is aryl or cycloalkyl wherein R^4 is substituted with 1, 2 or 3 substituents selected from paragraphs (C) and (D) hereinafter:

(C) hydroxy, halogeno, trifluoromethyl, cyano, mercapto, nitro, amino, carboxy, carbamoyl, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (1-6C)alkanoyl, cyano-(1-6C)alkyl, hydroxy-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkanoyloxy, (1-6C)alkanoylamino, (1-6C)alkoxycarbonylamino, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, aryl, aryl-(1-6C)alkyl, aryl-(1-6C)alkoxy, arylthio, arylsulphinyl, arylsulphonyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl and heterocyclyl-(1-6C)alkyl; and

(D) (1-3C)alkylenedioxy, halogeno-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, carboxy-(1-6C)alkyl, (1-6C)alkoxycarbonyl-(1-6C)alkyl, carbamoyl-(1-6C)alkyl, N-(1-6C)alkylcarbamoyl-(1-6C)alkyl, N,N-di-[(1-6C)alkyl]carbamoyl-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl, hydroxy-(2-6C)alkoxy-(1-6C)alkyl, (1-6C)alkoxy-(2-6C)alkoxy-(1-6C)alkyl, hydroxy-(2-6C)alkylamino-(1-6C)alkyl, (1-6C)alkoxy-(2-6C)alkylamino-(1-6C)alkyl, amino-(2-6C)alkylamino-(1-6C)alkyl, (1-6C)alkylamino-(2-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(2-6C)alkylamino-

(1-6C)alkyl, (1-6C)alkylthio-(1-6C)alkyl, hydroxy-(2-6C)alkylthio-(1-6C)alkyl, (1-6C)alkoxy-(2-6C)alkylthio-(1-6C)alkyl, halogeno-(2-6C)alkoxy, hydroxy-(2-6C)alkoxy, (1-6C)alkoxy-(2-6C)alkoxy, cyano-(1-6C)alkoxy, carboxy-(1-6C)alkoxy, (1-6C)alkoxycarbonyl-(1-6C)alkoxy, carbamoyl-(1-6C)alkoxy, N-(1-6C)alkylcarbamoyl-(1-6C)alkoxy, N,N-di-[(1-6C)alkyl]carbamoyl-(1-6C)alkoxy, amino-(2-6C)alkoxy, (1-6C)alkylamino-(2-6C)alkoxy, di-[(1-6C)alkyl]amino-(2-6C)alkoxy, halogeno-(2-6C)alkylamino, hydroxy-(2-6C)alkylamino, (1-6C)alkoxy-(2-6C)alkylamino, cyano-(1-6C)alkylamino, carboxy-(1-6C)alkylamino, (1-6C)alkoxycarbonyl-(1-6C)alkylamino, carbamoyl-(1-6C)alkylamino, N-(1-6C)alkylcarbamoyl-(1-6C)alkylamino, N,N-di-[(1-6C)alkyl]carbamoyl-(1-6C)alkylamino, amino-(2-6C)alkylamino, (1-6C)alkylamino-(2-6C)alkylamino, di-[(1-6C)alkyl]amino-(2-6C)alkylamino, N-(1-6C)alkyl-halogeno-(1-6C)alkylamino, N-(1-6C)alkyl-hydroxy-(2-6C)alkylamino, N-(1-6C)alkyl-(1-6C)alkoxy-(2-6C)alkylamino, N-(1-6C)alkyl-cyano-(1-6C)alkylamino, N-(1-6C)alkyl-carboxy-(1-6C)alkylamino, N-(1-6C)alkyl-(1-6C)alkoxycarbonyl-(1-6C)alkylamino, N-(1-6C)alkyl-carbamoyl-(1-6C)alkylamino, N-(1-6C)alkyl-N-(1-6C)alkylcarbamoyl-(1-6C)alkylamino, N-(1-6C)alkyl-N,N-di-[(1-6C)alkyl]carbamoyl-(1-6C)alkylamino, N-(1-6C)alkyl-amino-(2-6C)alkylamino, N-(1-6C)alkyl-(1-6C)alkylamino-(2-6C)alkylamino, N-(1-6C)alkyl-di-[(1-6C)alkyl]amino-(2-6C)alkylamino, (1-6C)alkanesulphonylamino, halogeno-(2-6C)alkanoylamino, hydroxy-(2-6C)alkanoylamino, (1-6C)alkoxy-(2-6C)alkanoylamino, cyano-(2-6C)alkanoylamino, carboxy-(2-6C)alkanoylamino, (1-6C)alkoxycarbonyl-(2-6C)alkanoylamino, carbamoyl-(2-6C)alkanoylamino, N-(1-6C)alkylcarbamoyl-(2-6C)alkanoylamino, N,N-di-[(1-6C)alkyl]carbamoyl-(2-6C)alkanoylamino, amino-(2-6C)alkanoylamino, (1-6C)alkylamino-(2-6C)alkanoylamino, di-[(1-6C)alkyl]amino- (2-6C)alkanoylamino, aryloxy, arylamino, aryl-(1-6C)alkylamino, N-(1-6C)alkyl-aryl-(1-6C)alkylamino, aroylamino, arylsulphonylamino, N-arylsulphamoyl, aryl-(2-6C)alkanoylamino, heteroaryloxy, heteroaryl-(1-6C)alkoxy, heteroarylamino, heteroaryl-(1-6C)alkylamino, N-(1-6C)alkyl-heteroaryl-(1-6C)alkylamino, heteroarylcarbonylamino, heteroarylsulphonylamino, N-heteroarylsulphamoyl, heteroaryl-(2-6C)alkanoylamino, heterocyclyloxy, heterocyclyl-(1-6C)alkoxy, heterocyclylamino, heterocyclyl-(1-6C)alkylamino, N-(1-6C)alkyl-heterocyclyl-(1-6C)alkylamino, heterocyclylcarbonylamino,

heterocyclylsulphonylamino, N-heterocyclylsulphamoyl and heterocyclyl-(2-6C)alkanoylamino, and wherein any aryl, heteroaryl or heterocyclyl group in a substituent on R^4 may optionally bear 1 or 2 substituents selected from halogeno, (1-6C)alkyl and (1-6C)alkoxy;

or a pharmaceutically-acceptable salt or in-vivo-cleavable ester thereof;

provided that a substituent on R^4 is selected from paragraph (C) hereinbefore only if at least one R^1 group is selected from paragraph (B) hereinbefore.

In this specification the generic term "alkyl" includes both straight-chain and branched-chain alkyl groups. However references to individual alkyl groups such as "propyl" are specific for the straight-chain version only and references to individual branched-chain alkyl groups such as "isopropyl" are specific for the branched-chain version only. An analogous convention applies to other generic terms.

It is to be understood that, insofar as certain of the compounds of Formula I defined above may exist in optically active or racemic forms by virtue of one or more asymmetric carbon atoms, the invention includes in its definition any such optically active or racemic form which possesses the property of inhibiting cytokines, in particular TNF. The synthesis of optically active forms may be carried out by standard techniques of organic chemistry well known in the art, for example by synthesis from optically active starting materials or by resolution of a racemic form. Similarly, inhibitory properties against TNF may be evaluated using the standard laboratory techniques referred to hereinafter.

Suitable values for the generic radicals referred to above include those set out below.

Suitable values for various R^3, R^1 or R^2 groups, or for various substituents on R^4 or on an aryl, heteroaryl or heterocyclyl group in R^1 or on a R^4 substituent include:-

for halogeno:	fluoro, chloro, bromo and iodo;
for (1-6C)alkyl:	methyl, ethyl, propyl, isopropyl and tert-butyl;
for (2-6C)alkenyl:	vinyl and allyl;
for (2-6C)alkynyl:	ethynyl and 2-propynyl;
for (1-6C)alkoxy:	methoxy, ethoxy, propoxy, isopropoxy and butoxy;
for (1-6C)alkylamino:	methylamino, ethylamino and propylamino;
for di-[(1-6C)alkyl]amino:	dimethylamino, diethylamino and

N-ethyl-N-methylamino.

Suitable values for R^1 from paragraph (A) above and for a substituent on R^4 from paragraph (C) above include:-

for (1-6C)alkylthio:	methylthio, ethylthio and propylthio;
for (1-6C)alkylsulphinyl:	methylsulphinyl, ethylsulphinyl and propylsulphinyl;
for (1-6C)alkylsulphonyl:	methylsulphonyl, ethylsulphonyl and propylsulphonyl;
for (1-6C)alkoxycarbonyl:	methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl and tert-butoxycarbonyl;
for N-(1-6C)alkylcarbamoyl:	N-methylcarbamoyl, N-ethylcarbamoyl and N-propylcarbamoyl;
for N,N-di-[(1-6C)alkyl]carbamoyl:	N,N-dimethylcarbamoyl, N-ethyl-N-methylcarbamoyl and N,N-diethylcarbamoyl;
for (1-6C)alkanoyl:	formyl, acetyl and propionyl;
for cyano-(1-6C)alkyl:	cyanomethyl, 2-cyanoethyl, 1-cyanoethyl and 3-cyanopropyl;
for hydroxy-(1-6C)alkyl:	hydroxymethyl, 2-hydroxyethyl, 1-hydroxyethyl and 3-hydroxypropyl;
for amino-(1-6C)alkyl:	aminomethyl, 2-aminoethyl, 1-aminoethyl and 3-aminopropyl;
for (1-6C)alkanoyloxy:	formyloxy, acetoxy and propionyloxy:
for (1-6C)alkanoylamino:	formamido, acetamido and propionamido;
for (1-6C)alkoxycarbonylamino:	methoxycarbonylamino;
for N-(1-6C)alkylsulphamoyl:	N-methylsulphamoyl and N-ethylsulphamoyl;
for N,N-di-[(1-6C)alkyl]sulphamoyl:	N,N-dimethylsulphamoyl.

A suitable value for R^1 or R^4 or for a substituent on R^4 when it is aryl or for the aryl group when R^1 or the substituent on R^4 is arylthio, arylsulphinyl or arylsulphonyl is, for example, phenyl or naphthyl, preferably phenyl; when it is aryl-(1-6C)alkyl is, for example, benzyl and 2-phenylethyl; and when it is aryl-(1-6C)alkoxy is, for example, benzyloxy and 2-phenylethoxy.

A suitable value for R^1 or for a substituent on R^4 when it is heteroaryl or for the heteroaryl group when R^1 or the substituent on R^4 is heteroaryl-(1-6C)alkyl is, for example, an aromatic 5- or 6-membered monocyclic ring or a 9- or 10-membered bicyclic ring with up to five ring heteroatoms selected from oxygen, nitrogen and sulphur, for example furyl, pyrrolyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,3,5-triazenyl, benzofuranyl, indolyl, benzothienyl, benzoxazolyl, benzimidazolyl, benzothiazolyl, indazolyl, quinolyl, isoquinolyl, quinazolinyl, quinoxalinyl or cinnolinyl. A heteroaryl-(1-6C)alkyl group may be, for example, a heteroarylmethyl or 2-heteroarylethyl group.

A suitable value for R^1 or for a substituent on R^4 when it is heterocyclyl or for the heterocyclyl group when R^1 or the substituent on R^4 is heterocyclyl-(1-6C)alkyl is, for example, a non-aromatic saturated or partially saturated 3 to 10 membered monocyclic or bicyclic ring with up to five heteroatoms selected from oxygen, nitrogen and sulphur, for example oxiranyl, oxetanyl, tetrahydropyranyl, pyrrolinyl, pyrrolidinyl, morpholinyl, piperidinyl, homopiperidinyl, piperazinyl, 4-(1-6C)alkylpiperazinyl (such as 4-methylpiperazinyl), homopiperazinyl, 4-(1-6C)alkylhomopiperazinyl, dihydropyridinyl, tetrahydropyridinyl, dihydropyrimidinyl or tetrahydropyrimidinyl. A heterocyclyl-(1-6C)alkyl group may be, for example, a heterocyclylmethyl or 2-heterocyclylethyl group.

Suitable values for R^1 from paragraph (B) above and for a substituent on R^4 from paragraph (D) above include:-

for (1-3C)alkylenedioxy:	methylenedioxy, ethylenedioxy and propylenedioxy;
for halogeno-(1-6C)alkyl:	fluoromethyl, chloromethyl, bromomethyl, difluoromethyl, dichloromethyl, dibromomethyl, 2-fluoroethyl, 2-chloroethyl and 2-bromoethyl;
for (1-4C)alkoxy-(1-6C)alkyl:	methoxymethyl, ethoxymethyl, 1-methoxyethyl, 2-methoxyethyl, 2-ethoxyethyl and 3-methoxypropyl;
for carboxy-(1-6C)alkyl:	carboxymethyl, 1-carboxyethyl, 2-carboxyethyl and 3-carboxypropyl;

for (1-6C)alkoxycarbonyl-(1-6C)alkyl: methoxycarbonylmethyl, ethoxycarbonylmethyl, tert-butoxycarbonylmethyl, 1-methoxycarbonylethyl, 1-ethoxycarbonylethyl, 2-methoxycarbonylethyl, 2-ethoxycarbonylethyl, 3-methoxycarbonylpropyl and 3-ethoxycarbonylpropyl;

for carbamoyl-(1-6C)alkyl: carbamoylmethyl, 1-carbamoylethyl, 2-carbamoylethyl and 3-carbamoylpropyl;

for N-(1-6C)alkylcarbamoyl-(1-6C)alkyl: N-methylcarbamoylmethyl, N-ethylcarbamoylmethyl, N-propylcarbamoylmethyl, 1-(N-methylcarbamoyl)ethyl, 1-(N-ethylcarbamoyl)ethyl, 2-(N-methylcarbamoyl)ethyl, 2-(N-ethylcarbamoyl)ethyl and 3-(N-methylcarbamoyl)propyl;

for N,N-di-[(1-6C)alkyl]carbamoyl-(1-6C)alkyl: N,N-dimethylcarbamoylmethyl, N-ethyl-N-methylcarbamoylmethyl, N,N-diethylcarbamoylmethyl, 1-(N,N-dimethylcarbamoyl)ethyl, 1-(N,N-diethylcarbamoyl)ethyl, 2-(N,N-dimethylcarbamoyl)ethyl, 2-(N,N-diethylcarbamoyl)ethyl and 3-(N,N-dimethylcarbamoyl)propyl;

for (1-6C)alkylamino-(1-6C)alkyl: methylaminomethyl, ethylaminomethyl, 1-methylaminoethyl, 2-methylaminoethyl, 2-ethylaminoethyl and 3-methylaminopropyl;

for di-[(1-6C)alkyl]amino-(1-6C)alkyl:	dimethylaminomethyl, diethylaminomethyl, 1-dimethylaminoethyl, 2-dimethylaminoethyl and 3-dimethylaminopropyl;
for hydroxy-(2-6C)alkoxy-(1-6C)alkyl:	2-hydroxyethoxymethyl, 3-hydroxypropoxymethyl and 2-(2-hydroxyethoxy)ethyl;
for (1-6C)alkoxy-(2-6C)alkoxy-(1-6C)alkyl:	2-methoxyethoxymethyl, 3-methoxypropoxymethyl and 2-(2-methoxyethoxy)ethyl;
for hydroxy-(2-6C)alkylamino-(1-6C)alkyl:	2-hydroxyethylaminomethyl, 3-hydroxypropylaminomethyl and 2-(2-hydroxyethylamino)ethyl;
for (1-6C)alkoxy-(2-6C)alkylamino-(1-6C)alkyl:	2-methoxyethylaminomethyl, 3-methoxypropylaminomethyl and 2-(2-methoxyethylamino)ethyl;
for amino-(2-6C)alkylamino-(1-6C)alkyl:	2-aminoethylaminomethyl, 3-aminopropylaminomethyl and 2-(2-aminoethylamino)ethyl;
for (1-6C)alkylamino-(2-6C)alkylamino-(1-6C)alkyl:	2-methylaminoethylaminomethyl, 3-ethylaminopropylaminomethyl and 2-(2-methylaminoethylamino)ethyl;
for di-[(1-6C)alkyl]amino-(2-6C)alkylamino-(1-6C)alkyl:	2-dimethylaminoethylaminomethyl, 3-dimethylaminopropylaminomethyl and 3-(2-diethylaminoethylamino)propyl;
for (1-6C)alkylthio-(1-6C)alkyl:	methylthiomethyl, 2-ethylthioethyl and 3-methylthiopropyl;
for hydroxy-(2-6C)alkylthio-(1-6C)alkyl:	2-hydroxyethylthiomethyl, 3-hydroxypropylthiomethyl and

2-(2-hydroxyethylthio)ethyl;

for (1-6C)alkoxy-(2-6C)alkylthio-(1-6C)alkyl: 2-methoxyethylthiomethyl, 3-methoxypropylthiomethyl and 2-(2-ethoxyethylthio)ethyl;

for hydroxy-N-(1-6C)alkyl-(2-6C)alkylamino-(1-6C)alkyl: N-methyl-2-hydroxyethylaminomethyl, N-ethyl-3-hydroxypropylaminomethyl and 2-(N-methyl-2-hydroxyethylamino)ethyl;

for (1-6C)alkoxy-N-(1-6C)alkyl-(2-6C)alkylamino-(1-6C)alkyl: N-methyl-2-methoxyethylaminomethyl, N-ethyl-3-methoxypropylaminomethyl and 2-(N-methyl-2-methoxyethylamino)ethyl;

for amino-N-(1-6C)alkyl-(2-6C)alkylamino-(1-6C)alkyl: N-methyl-N-(2-aminoethyl)aminomethyl, N-ethyl-N-(3-aminopropyl)aminomethyl and 2-[N-methyl-N-(2-aminoethyl)amino]ethyl;

for (1-6C)alkylamino-N-(1-6C)alkyl-(2-6C)alkylamino-(1-6C)alkyl: N-methyl-N-(2-methylaminoethyl)-aminomethyl, N-ethyl-N-(3-ethylaminopropyl)-aminomethyl and 2-[N-methyl-N-(2-methylaminoethyl)amino]ethyl;

for di-[(1-6C)alkyl]amino-N-(1-6C)alkyl-(2-6C)alkylamino-(1-6C)alkyl: N-methyl-2-dimethylaminoethylaminomethyl, N-ethyl-3-dimethylaminopropylaminomethyl and 3-(N-methyl-2-diethylaminoethylamino)propyl;

for halogeno-(2-6C)alkoxy: 2-chloroethoxy, 2-bromoethoxy and 3-chloropropoxy;

for hydroxy-(2-6C)alkoxy: 2-hydroxyethoxy, 3-hydroxypropoxy, 2-hydroxy-2-methylethoxy and

	4-hydroxybutoxy;
for (1-6C)alkoxy-(2-6C)alkoxy:	2-methoxyethoxy, 2-ethoxyethoxy, 3-methoxypropoxy, 2-methoxy-1-methylethoxy and 4-ethoxybutoxy;
for cyano-(1-6C)alkoxy:	cyanomethoxy, 2-cyanoethoxy and 3-cyanopropoxy;
for carboxy-(1-6C)alkoxy:	carboxymethoxy, 2-carboxyethoxy and 3-carboxypropoxy;
for (1-6C)alkoxycarbonyl-(1-6C)alkoxy:	methoxycarbonylmethoxy, ethoxycarbonylmethoxy, tert-butoxycarbonylmethoxy, 2-methoxycarbonylethoxy and 3-ethoxycarbonylpropoxy;
for carbamoyl-(1-6C)alkoxy:	carbamoylmethoxy and 2-carbamoylethoxy;
for N-(1-6C)alkylcarbamoyl-(1-6C)alkoxy:	N-methylcarbamoylmethoxy, 2-(N-ethylcarbamoyl)ethoxy and 3-(N-methylcarbamoyl)propoxy;
for N,N-di-[(1-6C)alkyl]carbamoyl-(1-6C)alkoxy:	N,N-dimethylcarbamoylmethoxy, 2-(N,N-dimethylcarbamoyl)ethoxy and 3-(N,N-diethylcarbamoyl)propoxy;
for amino-(2-6C)alkoxy:	2-aminoethoxy, 3-aminopropoxy and 4-aminobutoxy;
for (1-6C)alkylamino-(2-6C)alkoxy:	2-methylaminoethoxy, 2-methylamino-1-methylethoxy and 3-ethylaminopropoxy;
for di-[(1-6C)alkyl]amino-(2-6C)alkoxy:	2-dimethylaminoethoxy, 2-diethylaminoethoxy, 2-dimethylamino-2-methylethoxy and 3-dimethylaminopropoxy;
for halogeno-(2-6C)alkylamino:	2-fluoroethylamino, 2-chloroethylamino, 2-bromoethylamino, 3-fluoropropylamino and

	3-chloropropylamino;
for hydroxy-(2-6C)alkylamino:	2-hydroxyethylamino, 3-hydroxypropylamino and 4-hydroxybutylamino;
for (1-6C)alkoxy-(2-6C)alkylamino:	2-methoxyethylamino, 2-ethoxyethylamino, 3-methoxypropylamino and 3-ethoxypropylamino;
for cyano-(1-6C)alkylamino:	cyanomethylamino, 2-cyanoethylamino and 3-cyanopropylamino;
for carboxy-(1-6C)alkylamino:	carboxymethylamino, 2-carboxyethylamino and 3-carboxypropylamino;
for (1-6C)alkoxycarbonyl-(1-6C)alkylamino:	methoxycarbonylmethylamino, 2-(ethoxycarbonyl)ethylamino and 3-(tert-butoxycarbonyl)propylamino;
for carbamoyl-(1-6C)alkylamino:	carbamoylmethylamino and 2-carbamoylethylamino;
for N-(1-6C)alkylcarbamoyl-(1-6C)alkylamino:	N-methylcarbamoylmethylamino, N-ethylcarbamoylmethylamino and 2-(N-methylcarbamoyl)ethylamino;
for N,N-di-[(1-6C)alkyl]carbamoyl-(1-6C)alkylamino:	N,N-dimethylcarbamoylmethylamino, N,N-diethylcarbamoylmethylamino and 2-(N,N-dimethylcarbamoyl)ethylamino;
for amino-(2-6C)alkylamino:	2-aminoethylamino and 3-aminopropylamino;
for (1-6C)alkylamino-(2-6C)alkylamino:	2-methylaminoethylamino, 2-ethylaminoethylamino, 2-propylaminoethylamino, 3-methylaminopropylamino, 3-ethylaminopropylamino and 4-methylaminobutylamino;

for di-[(1-6C)alkyl]amino-(2-6C)alkylamino: 2-dimethylaminoethylamino, 2-(N-ethyl-N-methylamino)ethylamino, 2-diethylaminoethylamino, 2-dipropylaminoethylamino, 3-dimethylaminopropylamino, 3-diethylaminopropylamino and 4-dimethylaminobutylamino;

for N-(1-6C)alkyl-halogeno-(2-6C)alkylamino: N-(2-chloroethyl)-N-methylamino, N-(2-bromoethyl)-N-methylamino and N-(2-bromoethyl)-N-ethylamino;

for N-(1-6C)alkyl-hydroxy-(2-6C)alkylamino: N-(2-hydroxyethyl)-N-methylamino, N-(3-hydroxypropyl)-N-methylamino and N-ethyl-N-(2-hydroxyethyl)amino;

for N-(1-6C)alkyl-(1-6C)alkoxy-(2-6C)alkylamino: N-methyl-N-(2-methoxyethyl)amino, N-methyl-N-(3-methoxypropyl)amino and N-ethyl-N-(2-methoxyethyl)amino;

for N-(1-6C)alkyl-cyano-(1-6C)alkylamino: N-(cyanomethyl)-N-methylamino;

for N-(1-6C)alkyl-carboxy-(1-6C)alkylamino: N-carboxymethyl-N-methylamino and N-(2-carboxyethyl)-N-methylamino;

for N-(1-6C)alkyl-(1-6C)alkoxycarbonyl-(1-6C)alkylamino: N-methoxycarbonylmethyl-N-methylamino, N-(2-ethoxycarbonylethyl)-N-ethylamino and N-(2-tert-butoxycarbonylethyl)-N-methylamino;

for N-(1-6C)alkyl-carbamoyl-(1-6C)alkylamino: N-carbamoylmethyl-N-methylamino and N-(2-carbamoylethyl)-N-methylamino;

for N-(1-6C)alkyl-N-(1-6C)alkylcarbamoyl-(1-6C)alkylamino: N-(N-methylcarbamoylmethyl)-N-methylamino, N-(N-ethylcarbamoylmethyl)-N-methylamino and N-[2-(N-methylcarbamoyl)ethyl]-N-methylamino;

for N-(1-6C)alkyl-N,N-di-[(1-6C)alkyl]carbamoyl-(1-6C)alkylamino: N-(N,N-dimethylcarbamoylmethyl)-N-methylamino and N-[2-(N,N-dimethylcarbamoyl)ethyl]-N-methylamino;

for N-(1-6C)alkyl-amino-(2-6C)alkylamino: N-(2-aminoethyl)-N-methylamino and N-(3-aminopropyl)-N-methylamino;

for N-(1-6C)alkyl-(1-6C)alkylamino-(2-6C)alkylamino: N-(2-methylaminoethyl)-N-methylamino and N-(3-ethylaminopropyl)-N-ethylamino;

for N-(1-6C)alkyl-di-[(1-6C)alkyl]amino-(2-6C)alkylamino: N-(2-dimethylaminoethyl)-N-methylamino, N-(2-diethylaminoethyl)-N-methylamino and N-(3-dimethylaminopropyl)-N-methylamino;

for (1-6C)alkanesulphonylamino: methanesulphonylamino and ethanesulphonylamino;

for N-(1-6C)alkyl-(1-6C)alkanesulphonylamino: N-methylmethanesulphonylamino and N-methylethanesulphonylamino;

for halogeno-(2-6C)alkanoylamino: 2-chloroacetamido and 3-chloropropionamido;

for hydroxy-(2-6C)alkanoylamino: 2-hydroxyacetamido and 3-hydroxypropionamido;

for (1-6C)alkoxy-(2-6C)alkanoylamino: 2-methoxyacetamido and 3-methoxypropionamido;

for cyano-(2-6C)alkanoylamino: 2-cyanoacetamido and 3-cyanopropionamido;

for carboxy-(2-6C)alkanoylamino: 2-carboxyacetamido and 3-carboxypropionamido;

for (1-6C)alkoxycarbonyl-(2-6C)alkanoyl:	2-methoxycarbonylacetamido, 2-(tert-butoxycarbonyl)acetamido and 3-methoxycarbonylpropionamido;
for carbamoyl-(2-6C)alkanoylamino:	2-carbamoylacetamido, 3-carbamoylpropionamido and 4-carbamoylbutyramido;
for N-(1-6C)alkylcarbamoyl-(2-6C)alkanoylamino:	2-(N-methylcarbamoyl)acetamido and 3-(N-ethylcarbamoyl)propionamido;
for N,N-di-[(1-6C)alkyl]carbamoyl-(2-6C)alkanoylamino:	2-(N,N-dimethylcarbamoyl)acetamido, 2-(N,N-diethylcarbamoyl)acetamido and 3-(N,N-dimethylcarbamoyl)propionamido;
for amino-(2-6C)alkanoylamino:	2-aminoacetamido, 2-aminopropionamido and 3-aminopropionamido;
for (1-6C)alkylamino-(2-6C)alkanoylamino:	2-methylaminoacetamido, 2-ethylaminoacetamido, 2-methylaminopropionamido and 3-methylaminopropionamido;
for di-[(1-6C)alkyl]amino-(2-6C)alkanoylamino:	2-dimethylaminoacetamido, 2-diethylaminoacetamido, 2-dimethylaminopropionamido and 3-dimethylaminopropionamido;
for aryl-(1-6C)alkylamino:	benzylamino and 2-phenethylamino;
for N-(1-6C)alkyl-aryl-(1-6C)alkylamino:	N-benzyl-N-methylamino;
for aroylamino:	benzamido and 2-naphthoylamino;
for aryl-(2-6C)alkanoylamino:	phenylacetamido and 3-phenylpropionamido;
for aryl-(1-6C)alkoxy-(1-6C)alkyl:	benzyloxymethyl and 2-benzyloxyethyl;
for aryl-(1-6C)alkylamino-(1-6C)alkyl:	benzylaminomethyl and 2-benzylaminoethyl;

for N-(1-6C)alkyl-aryl-(1-6C)alkylamino-(1-6C)alkyl:	N-benzyl-N-methylaminomethyl;
for heteroaryl-(1-6C)alkoxy:	heteroarylmethoxy and 2-heteroarylethoxy;
for heteroaryl-(1-6C)alkylamino:	heteroarylmethylamino and 2-heteroarylethylamino;
for N-(1-6C)alkyl-heteroaryl-(1-6C)alkylamino:	N-heteroarylmethyl-N-methylamino and N-(2-heteroarylethyl)-N-methylamino;
for heteroaryl-(2-6C)alkanoylamino:	2-heteroarylacetamido and 3-heteroarylpropionamido;
for heteroaryl-(1-6C)alkoxy-(1-6C)alkyl:	heteroarylmethoxymethyl and 2-heteroarylethoxymethyl;
for heteroaryl-(1-6C)alkylamino-(1-6C)alkyl:	heteroarylmethylaminomethyl and 2-heteroarylethylaminomethyl;
for N-(1-6C)alkyl-heteroaryl-(1-6C)alkylamino-(1-6C)alkyl:	N-heteroarylmethyl-N-methylaminomethyl and N-(2-heteroarylethyl)-N-methylaminomethyl;
for heterocyclyl-(1-6C)alkoxy:	heterocyclylmethoxy, 2-heterocyclylethoxy, 3-heterocyclylpropoxy and 2-heterocyclyl-2-methylethoxy;
for heterocyclyl-(1-6C)alkylamino:	heterocyclylmethylamino, 2-heterocyclylethylamino and 3-heterocyclylpropylamino;
for N-(1-6C)alkyl-heterocyclyl-(1-6C)alkylamino:	N-heterocyclylmethyl-N-methylamino and N-(2-heterocyclylethyl)-N-methylamino;
for heterocyclyl-(2-6C)alkanoylamino:	2-heterocyclylacetamido, 2-heterocyclylpropionamido and

3-heterocyclylpropionamido;

for heterocyclyl-(1-6C)alkoxy-(1-6C)alkyl: heterocyclylmethoxymethyl and 2-heterocyclylethoxymethyl;

for heterocyclyl-(1-6C)alkylamino-(1-6C)alkyl: heterocyclylmethylaminomethyl and 2-heterocyclylethylaminomethyl;

for N-(1-6C)alkyl-heterocyclyl-(1-6C)alkylamino-(1-6C)alkyl: N-heterocyclylmethyl-N-methylaminomethyl and N-(2-heterocyclylethyl)-N-methylaminomethyl;

When any of the substituents defined in paragraphs (B) or (D) hereinbefore which comprise a CH_2 group which is attached to 2 carbon atoms or a CH_3 group which is attached to a carbon atom may optionally bear on each said CH_2 or CH_3 group a substituent selected from hydroxy, amino, (1-6C)alkoxy, (1-6C)alkylamino and di-[(1-6C)alkyl]amino, suitable substituents so formed include, for example, substituted heterocyclyl-(1-6C)alkoxy groups such as 2-hydroxy-3-piperidinopropoxy and 2-hydroxy-3-morpholinopropoxy, substituted (1-6C)alkylamino-(2-6C)alkoxy such as 2-hydroxy-3-methylaminopropoxy and substituted di-[(1-6C)alkyl]amino-(2-6C)alkoxy such as 3-dimethylamino-2-hydroxypropoxy, 3-[N-(3-dimethylaminopropyl)-N-methylamino]propoxy and 3-[N-(3-dimethylaminopropyl)-N-methylamino]-2-hydroxypropoxy.

A suitable value for the aryl group when R^1 or the substituent on R^4 is aryloxy, arylamino, aryl-(1-6C)alkylamino, N-(1-6C)alkyl-aryl-(1-6C)alkylamino, aroylamino, arylsulphonylamino, N-arylsulphamoyl or aryl-(2-6C)alkanoylamino is phenyl or naphthyl, preferably phenyl.

A suitable value for the heteroaryl group when R^1 or the substituent on R^4 is, for example, heteroaryloxy or any of the other specified heteroaryl-containing groups is any of the suitable heteroaryl groups defined hereinbefore.

A suitable value for the heterocyclyl group when R^1 or the substituent on R^4 is, for example, heterocyclylamino or any of the other specified heterocyclyl-containing groups is any of the suitable heterocyclyl groups defined hereinbefore.

A suitable value for R^4 when it is cycloalkyl is, for example, a non-aromatic mono-

or bicyclic 5- to 10-membered carbon ring such as cyclopentyl, cyclohexyl, cycloheptyl, bicyclo[2.2.1]heptyl and bicyclo[4.4.0]decyl.

A suitable pharmaceutically-acceptable salt of a compound of the Formula I is, for example, an acid-addition salt of a compound of the Formula I which is sufficiently basic, for example an acid-addition salt with an inorganic or organic acid such as hydrochloric, hydrobromic, sulphuric, trifluoroacetic, citric or maleic acid; or, for example a salt of a compound of the Formula I which is sufficiently acidic, for example an alkali or alkaline earth metal salt such as a calcium or magnesium salt, or an ammonium salt, or a salt with an organic base such as methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

Various forms of prodrugs are known in the art. For examples of such prodrug derivatives, see:

a) Design of Prodrugs, edited by H. Bundgaard, (Elsevier, 1985) and Methods in Enzymology, Vol. 42, p. 309-396, edited by K. Widder, *et al.* (Academic Press, 1985);

b) A Textbook of Drug Design and Development, edited by Krogsgaard-Larsen and H. Bundgaard, Chapter 5 "Design and Application of Prodrugs", by H. Bundgaard p. 113-191 (1991);

c) H. Bundgaard, Advanced Drug Delivery Reviews, 8, 1-38 (1992);

d) H. Bundgaard, *et al.*, Journal of Pharmaceutical Sciences, 77, 285 (1988); and

e) N. Kakeya, *et al.*, Chem. Pharm. Bull., 32, 692 (1984).

Examples of such pro-drugs may be used to form in-vivo-cleavable esters of a compound of the Formula I. An in-vivo-cleavable ester of a compound of the Formula I containing a carboxy group is, for example, a pharmaceutically-acceptable ester which is cleaved in the human or animal body to produce the parent acid. Suitable pharmaceutically-acceptable esters for carboxy include (1-6C)alkoxymethyl esters, for example methoxymethyl; (1-6C)alkanoyloxymethyl esters, for example pivaloyloxymethyl; phthalidyl esters; (3-8C)cycloalkoxycarbonyloxyC_{1-6}alkyl esters, for example 1-cyclohexylcarbonyloxyethyl; 1,3-dioxolan-2-ylmethyl esters, for example 5-methyl-1,3-dioxolan-2-ylmethyl; and (1-6C)alkoxycarbonyloxyethyl esters, for example 1-methoxycarbonyloxyethyl; and may be formed at any carboxy group in the compounds of this invention.

Particular novel compounds of the invention include, for example, amide derivatives of the Formula I, or pharmaceutically-acceptable salts thereof, wherein:-

(a) R^3 is (1-6C)alkyl such as methyl, ethyl, propyl and isopropyl, preferably methyl and ethyl, more preferably methyl; and R^1, R^2, R^4, m, p and q have any of the meanings defined hereinbefore or in this section relating to particular novel compounds of the invention;

(b) R^3 is halogeno such as fluoro, bromo and chloro, preferably chloro and bromo, more preferably chloro; and R^1, R^2, R^4, m, p and q have any of the meanings defined hereinbefore or in this section relating to particular novel compounds of the invention;

(c) R^1 is selected from the substituents defined in paragraphs (A) and (B) hereinafter:-

(A) hydroxy, halogeno, trifluoromethyl, cyano, (1-6C)alkyl, (1-6C)alkoxy and amino-(1-6C)alkyl; and

(B) halogeno-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl, hydroxy-(2-6C)alkylamino-(1-6C)alkyl, (1-6C)alkoxy-(2-6C)alkylamino-(1-6C)alkyl, halogeno-(2-6C)alkoxy, hydroxy-(2-6C)alkoxy, (1-6C)alkoxy-(2-6C)alkoxy, cyano-(1-6C)alkoxy, carboxy-(1-6C)alkoxy, (1-6C)alkoxycarbonyl-(1-6C)alkoxy, amino-(2-6C)alkoxy, (1-6C)alkylamino-(2-6C)alkoxy, di-[(1-6C)alkyl]amino-(2-6C)alkoxy, pyridyl-(1-6C)alkoxy, imidazolyl-(1-6C)alkoxy, piperidinyloxy, 1-(1-6C)alkylpiperidinyloxy, pyrrolidinyl-(2-6C)alkoxy, piperidinyl-(2-6C)alkoxy, morpholinyl-(2-6C)alkoxy, piperazinyl-(2-6C)alkoxy and 4-(1-6C)alkylpiperazinyl-(2-6C)alkoxy; and m is 1 or 2; and R^2, R^3, R^4, p and q have any of the meanings defined hereinbefore or in this section relating to particular novel compounds of the invention;

(d) q is 0, and R^4 is phenyl which is substituted with 1, 2 or 3 substituents selected from paragraphs (C) and (D) hereinafer:-

(C) hydroxy, halogeno, trifluoromethyl, cyano, amino, (1-6C)alkyl, (1-6C)alkoxy, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, phenyl, benzyl, benzyloxy, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, 4-(1-6C)alkylpiperazinyl, pyrrolidinyl-(1-6C)alkyl, piperidinyl-(1-6C)alkyl, morpholinyl-(1-6C)alkyl, piperazinyl-(1-6C)alkyl and 4-(1-6C)alkylpiperazinyl-(1-6C)alkyl; and

(D) halogeno-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl, hydroxy-(2-6C)alkylamino-(1-6C)alkyl,

(1-6C)alkoxy-(2-6C)alkylamino-(1-6C)alkyl, halogeno-(2-6C)alkoxy, hydroxy-(2-6C)alkoxy, (1-6C)alkoxy-(2-6C)alkoxy, cyano-(2-6C)alkoxy, carboxy-(2-6C)alkoxy, (1-6C)alkoxycarbonyl-(1-6C)alkoxy, amino-(2-6C)alkoxy, (1-6C)alkylamino-(2-6C)alkoxy, di-[(1-6)alkyl]amino-(2-6C)alkoxy, halogeno-(2-6C)alkylamino, hydroxy-(2-6C)alkylamino, (1-6C)alkoxy-(2-6C)alkylamino, amino-(2-6C)alkylamino, (1-6C)alkylamino-(2-6C)alkylamino, di-[(1-6C)alkyl]amino-(2-6C)alkylamino, N-(1-6C)alkyl-halogeno-(2-6C)alkylamino, N-(1-6C)alkyl-hydroxy-(2-6C)alkylamino, N-(1-6C)alkyl-(1-6C)alkoxy-(2-6C)alkylamino, N-(1-6C)alkyl-amino-(2-6C)alkylamino, N-(1-6C)alkyl-(1-6C)alkylamino-(2-6C)alkylamino, N-(1-6C)alkyl-di-[(1-6C)alkyl]amino-(2-6C)alkylamino, pyridyl-(1-6C)alkoxy, imidazolyl-(1-6C)alkoxy, piperidinyloxy, 1-(1-6C)alkylpiperidinyloxy, pyrrolidinyl-(2-6C)alkoxy, piperidinyl-(2-6C)alkoxy, morpholinyl-(2-6C)alkoxy, piperazinyl-(2-6C)alkoxy and 4-(1-6C)alkylpiperazinyl-(2-6C)alkoxy;

provided that a substituent on R^4 is selected from paragraph (C) hereinbefore only if at least one R^1 group is selected from paragraph (B) within section (c) of this section relating to particular novel compounds of the invention; and R^2, R^3, m and p have any of the meanings defined hereinbefore or in this section relating to particular novel compounds of the invention;

(e) p is 0; and R^1, R^3, R^4, m and q have any of the meanings defined hereinbefore or in this section relating to particular novel compounds of the invention; and

(f) q is 1, 2, 3 or 4, and R^4 is cycloalkyl; and R^1, R^2, R^3, m and p have any of the meanings defined hereinbefore or in this section relating to particular novel compounds of the invention.

A preferred compound of the invention is an amide derivative of the Formula I wherein R^3 is methyl, ethyl, chloro or bromo;

R^1 is selected from the substituents defined in paragraphs (A) and (B) hereinafter:-

(A) hydroxy, fluoro, chloro, trifluoromethyl, cyano, methyl, ethyl, methoxy and ethoxy; and

(B) chloromethyl, methoxymethyl, methylaminomethyl, ethylaminomethyl, dimethylaminomethyl, diethylaminomethyl, 2-hydroxyethylaminomethyl, 2-methoxyethylaminomethyl, 2-chloroethoxy, 3-chloropropoxy, 2-hydroxyethoxy, 3-hydroxypropoxy, 2-methoxyethoxy, 2-ethoxyethoxy, 3-methoxypropoxy, 3-ethoxypropoxy, cyanomethoxy, carboxymethoxy, 2-carboxyethoxy, methoxycarbonylmethoxy, ethoxycarbonylmethoxy, tert-butoxycarbonylmethoxy,

2-methoxycarbonylethoxy, 2-ethoxycarbonylethoxy, 2-tert-butoxycarbonylethoxy, 2-aminoethoxy, 3-aminopropoxy, 2-methylaminoethoxy, 2-ethylaminoethoxy, 3-methylaminopropoxy, 3-ethylaminopropoxy, 2-dimethylaminoethoxy, 2-diethylaminoethoxy, 3-dimethylaminopropoxy, 3-diethylaminopropoxy, 2-pyridylmethoxy, 2-(imidazol-1-yl)ethoxy, 3-(imidazol-1-yl)propoxy, piperidin-4-yloxy, 1-methylpiperidin-4-yloxy, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 2-(4-methylpiperazin-1-yl)ethoxy and 3-(4-methylpiperazin-1-yl)propoxy;

m is 1 or 2;

p is 0;

q is 0; and

R^4 is phenyl wherein R^4 is substituted with 1 or 2 substituents selected from paragraphs (C) and (D) hereinafter:-

(C) hydroxy, fluoro, chloro, trifluoromethyl, cyano, methyl, ethyl, methoxy, ethoxy, methylamino, ethylamino, dimethylamino, diethylamino, phenyl, benzyl, benzyloxy, pyrrolidin-1-yl, piperidino, morpholino, piperazin-1-yl and 4-methylpiperazin-1-yl; and

(D) chloromethyl, methoxymethyl, 2-methoxyethyl, methylaminomethyl, ethylaminomethyl, dimethylaminomethyl, diethylaminomethyl, 2-hydroxyethylaminomethyl, 2-methoxyethylaminomethyl, 2-chloroethoxy, 3-chloropropoxy, 2-hydroxyethoxy, 3-hydroxypropoxy, 2-methoxyethoxy, 2-ethoxyethoxy, 3-methoxypropoxy, 3-ethoxypropoxy, cyanomethoxy, carboxymethoxy, 2-carboxyethoxy, methoxycarbonylmethoxy, ethoxycarbonylmethoxy, tert-butoxycarbonylmethoxy, 2-methoxycarbonylethoxy, 2-ethoxycarbonylethoxy, 2-tert-butoxycarbonylethoxy, 2-aminoethoxy, 3-aminopropoxy, 2-methylaminoethoxy, 2-ethylaminoethoxy, 3-methylaminopropoxy, 3-ethylaminopropoxy, 2-dimethylaminoethoxy, 2-diethylaminoethoxy, 3-dimethylaminopropoxy, 3-diethylaminopropoxy, 2-chloroethylamino, 2-hydroxyethylamino, 2-methoxyethylamino, 2-ethoxyethylamino, 2-aminoethylamino, 2-methylaminoethylamino, 2-ethylaminoethylamino, 2-dimethylaminoethylamino, 2-diethylaminoethylamino, N-(2-chloroethyl)-N-methylamino, N-(2-hydroxyethyl)-N-methylamino, N-(2-methoxyethyl)-N-methylamino, N-(2-ethoxyethyl)-N-methylamino, N-(2-aminoethyl)-N-methylamino,

N-(2-methylaminoethyl)-N-methylamino, N-(2-dimethylaminoethyl)-N-methylamino, N-(3-aminopropyl)-N-methylamino, N-(3-methylaminopropyl)-N-methylamino, N-(3-ethylaminopropyl)-N-methylamino, N-(3-dimethylaminopropyl)-N-methylamino, N-(3-diethylaminopropyl)-N-methylamino, 2-pyridylmethoxy, 2-(imidazol-1-yl)ethoxy, 3-(imidazol-1-yl)propoxy, piperidin-4-yloxy, 1-methylpiperidin-4-yloxy, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 2-(4-methylpiperazin-1-yl)ethoxy and 3-(4-methylpiperazin-1-yl)propoxy; provided that a substituent on R^4 is selected from paragraph (C) immediately above only if at least one R^1 group is selected from paragraph (B) within the R^1 definition immediately above; or a pharmaceutically-acceptable salt thereof.

A further preferred compound of the invention is an amide derivative of the Formula I wherein R^3 is methyl or chloro;

R^1 is selected from the substituents defined in paragraphs (A) and (B) hereinafter:-

(A) methoxy; and

(B) chloromethyl, dimethylaminomethyl, diethylaminomethyl, 2-methoxyethylaminomethyl, 2-methoxyethoxy, 2-ethoxyethoxy, 3-methoxypropoxy, 3-ethoxypropoxy, methoxycarbonylmethoxy, ethoxycarbonylmethoxy, tert-butoxycarbonylmethoxy, 2-pyridylmethoxy, 2-(imidazol-1-yl)ethoxy, 2-pyrrolidin-1-ylethoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 2-morpholinoethoxy and 3-morpholinopropoxy;

m is 1 or 2;

p is 0;

q is 0; and

R^4 is phenyl wherein R^4 is substituted with 1 or 2 substituents selected from paragraphs (C) and (D) hereinafter:-

(C) cyano and dimethylamino; and

(D) chloromethyl, 2-chloroethoxy, 3-chloropropoxy, 2-hydroxyethoxy, 3-hydroxypropoxy, 2-methoxyethoxy, 2-ethoxyethoxy, 3-methoxypropoxy, 3-ethoxypropoxy, carboxymethoxy, methoxycarbonylmethoxy, ethoxycarbonylmethoxy, tert-butoxycarbonylmethoxy, 2-dimethylaminoethoxy, 2-diethylaminoethoxy,

3-dimethylaminopropoxy, 3-diethylaminopropoxy, N-(3-dimethylaminopropyl)-N-methylamino, 2-pyridylmethoxy, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 2-morpholinoethoxy and 3-morpholinopropoxy; provided that a substituent on R^4 is selected from paragraph (C) immediately above only if at least one R^1 group is selected from paragraph (B) within the R^1 definition immediately above; or a pharmaceutically-acceptable salt thereof.

A more preferred compound of the invention is an amide derivative of the Formula I wherein R^3 is methyl or chloro;

p is 0;

q is 0;

m is 1 or 2;

R^1 is selected from the substituents defined in paragraphs (A) and (B) hereinafter:-

(A) methoxy; and

(B) chloromethyl, diethylaminomethyl, 2-methoxyethylaminomethyl, 2-methoxyethoxy, 2-ethoxyethoxy, tert-butoxycarbonylmethoxy, methoxycarbonylmethoxy, 2-pyridylmethoxy, 2-(imidazol-1-yl)ethoxy, 2-pyrrolidin-1-ylethoxy, 2-morpholinoethoxy and 3-morpholinopropoxy; and

R^4 is phenyl which is substituted with one substituent selected from paragraphs (C) and (D) hereinafter:-

(C) cyano and dimethylamino; and

(D) chloromethyl, 3-chloropropoxy, 3-hydroxypropoxy, N-(3-dimethylaminopropyl)-N-methylamino, 2-pyridylmethoxy and 2-morpholinoethoxy; provided that the substituent on R^4 is selected from paragraph (C) immediately above only if at least R^1 group is selected from paragraph (B) within the R^1 definition immediately above; or a pharmaceutically-acceptable salt thereof.

A further more preferred compound of the invention is an amide derivative of the Formula I wherein R^3 is methyl or chloro;

p is 0;

q is 0;

m is 1 or 2; and

R^1 is methoxy and R^4 is phenyl which is substituted with one 3-hydroxypropoxy substituent,

or R^1 is 2-methoxyethoxy or 2-(imidazol-1-yl)ethoxy and R^4 is phenyl which is substituted with one cyano or dimethylamino substituent;
or a pharmaceutically-acceptable salt thereof.

Particular preferred compounds of the invention include, for example:-
N-{5-[4-(3-hydroxypropoxy)benzamido]-2-methylphenyl}-3,4-dimethoxybenzamide,
N-[5-(3-dimethylaminobenzamido)-2-methylphenyl]-4-(2-methoxyethoxy)benzamide,
N-[5-(4-cyanobenzamido)-2-methylphenyl]-4-(2-methoxyethoxy)benzamide and
N-[2-chloro-5-(4-cyanobenzamido)phenyl]-4-[2-(imidazol-1-yl)ethoxy]benzamide;
or the pharmaceutically-acceptable salts thereof.

In a further aspect of the present invention there is provided a group of novel compounds of the Formula I wherein $(R^1)_m$ represents a basic substituent located at the 3- and/or 4-positions and R^4 is phenyl which also bears a basic substituent located at the 3- and/or 4-positions. This group of compounds possesses improved TNFα inhibitory potency in one or both of the PBMC and Human Whole Blood tests described hereinafter.

A particular group of novel compounds according to this aspect of the invention is an amide derivative of the Formula I
wherein m is 1, the R^1 group is selected from the substituents defined in paragraph (B) hereinafter and the R^1 group is located at the 3- or 4-position,
or m is 2, at least one R^1 group is selected from the substituents defined in paragraph (B) hereinafter and one R^1 group may be selected from the substituents defined in paragraph (A) hereinafter and the R^1 groups, which may be the same or different, are located at the 3- and 4-positions :-

(A) hydroxy, fluoro, chloro, trifluoromethyl, cyano, amino, methyl, ethyl, methoxy, ethoxy, methylamino, ethylamino, dimethylamino, diethylamino, aminomethyl, 2-aminoethyl, pyrrolidin-1-yl, piperidino, morpholino, piperazin-1-yl, 4-methylpiperazin-1-yl, pyrrolidin-1-ylmethyl, piperidinomethyl, morpholinomethyl, piperazin-1-ylmethyl and 4-methylpiperazin-1-ylmethyl; and

(B) methylaminomethyl, ethylaminomethyl, dimethylaminomethyl, diethylaminomethyl, 2-hydroxyethylaminomethyl, 2-methoxyethylaminomethyl, 2-aminoethoxy, 3-aminopropoxy, 2-methylaminoethoxy, 2-ethylaminoethoxy, 3-methylaminopropoxy, 3-ethylaminopropoxy, 2-dimethylaminoethoxy,

2-diethylaminoethoxy, 3-dimethylaminopropoxy, 3-diethylaminopropoxy, 2-pyridylmethoxy, 2-(imidazol-1-yl)ethoxy, 3-(imidazol-1-yl)propoxy, piperidin-4-yloxy, 1-methylpiperidin-4-yloxy, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 2-(4-methylpiperazin-1-yl)ethoxy and 3-(4-methylpiperazin-1-yl)propoxy;

p is 0;

R^3 is methyl;

q is 0; and

R^4 is phenyl which is substituted with 1 substituent selected from those defined in paragraph (D) hereinafter and located at the 3- or 4-position,

or R^4 is phenyl which is substituted with 2 substituents, at least one selected from the substituents defined in paragraph (D) hereinafter and one optionally selected from the substituents defined in paragraph (C) hereinafter and the substituents, which may be the same or different, are located at the 3- and 4-positions :-

(C) hydroxy, fluoro, chloro, trifluoromethyl, cyano, amino, methyl, ethyl, methoxy, ethoxy, methylamino, ethylamino, dimethylamino, diethylamino, aminomethyl, 2-aminoethyl, pyrrolidin-1-yl, piperidino, morpholino, piperazin-1-yl, 4-methylpiperazin-1-yl, pyrrolidin-1-ylmethyl, piperidinomethyl, morpholinomethyl, piperazin-1-ylmethyl and 4-methylpiperazin-1-ylmethyl; and

(D) methylaminomethyl, ethylaminomethyl, dimethylaminomethyl, diethylaminomethyl, 2-hydroxyethylaminomethyl, 2-methoxyethylaminomethyl, 2-aminoethoxy, 3-aminopropoxy, 2-methylaminoethoxy, 2-ethylaminoethoxy, 3-methylaminopropoxy, 3-ethylaminopropoxy, 2-dimethylaminoethoxy, 2-diethylaminoethoxy, 3-dimethylaminopropoxy, 3-diethylaminopropoxy, 2-pyridylmethoxy, 2-(imidazol-1-yl)ethoxy, 3-(imidazol-1-yl)propoxy, piperidin-4-yloxy, 1-methylpiperidin-4-yloxy, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 2-(4-methylpiperazin-1-yl)ethoxy and 3-(4-methylpiperazin-1-yl)propoxy;

or a pharmaceutically-acceptable salt thereof;
provided that a substituent on R^4 is selected from paragraph (C) hereinbefore only if at least one R^1 group is selected from paragraph (B) hereinbefore.

A further particular group of novel compounds according to this aspect of the invention is an amide derivative of the Formula I
wherein m is 1, the R^1 group is selected from the substituents defined in paragraph (B) hereinafter and the R^1 group is located at the 3- or 4-position,
or m is 2 or 3, at least one R^1 group is selected from the substituents defined in paragraph (B) hereinafter and is located at the 3- or 4-position and the other R^1 groups, which may be the same or different, are selected from the substituents defined in paragraphs (A) or (B) hereinafter :-

(A) hydroxy, fluoro, chloro, trifluoromethyl, cyano, amino, methyl, ethyl, methoxy, ethoxy, methylamino, ethylamino, dimethylamino, diethylamino, aminomethyl, 2-aminoethyl, pyrrolidin-1-yl, piperidino, morpholino, piperazin-1-yl, 4-methylpiperazin-1-yl, pyrrolidin-1-ylmethyl, piperidinomethyl, morpholinomethyl, piperazin-1-ylmethyl and 4-methylpiperazin-1-ylmethyl; and

(B) methylaminomethyl, ethylaminomethyl, dimethylaminomethyl, diethylaminomethyl, 2-hydroxyethylaminomethyl, 2-methoxyethylaminomethyl, 2-aminoethoxy, 3-aminopropoxy, 2-methylaminoethoxy, 2-ethylaminoethoxy, 3-methylaminopropoxy, 3-ethylaminopropoxy, 2-dimethylaminoethoxy, 2-diethylaminoethoxy, 2-diisopropylaminoethoxy, 3-dimethylaminopropoxy, 3-diethylaminopropoxy, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 2-(N-methylpyrrolidin-2-yl)ethoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 2-(4-methylpiperazin-1-yl)ethoxy, 3-(4-methylpiperazin-1-yl)propoxy, 2-pyridylmethoxy, 2-methylthiazol-4-ylmethoxy, 2-(imidazol-1-yl)ethoxy, 3-(imidazol-1-yl)propoxy, piperidin-4-yloxy, N-methylpiperidin-4-yloxy, N-methylhomopiperidin-4-yloxy, pyrrolidin-3-yloxy and N-methylpyrrolidin-3-yloxy;

p is 0;

R^3 is methyl;

q is 0; and

R^4 is phenyl which is substituted with 1, 2 or 3 substituents, which may be the same or different, selected from the substituents defined in paragraphs (C1), (C2) or (D) hereinafter provided that one substituent is selected from the substituents defined in paragraphs (C2) or (D) hereinafter and is located at the 3- or 4-position :-

(C1) hydroxy, fluoro, chloro, trifluoromethyl, cyano, methyl, ethyl, methoxy and ethoxy;

(C2) amino, methylamino, ethylamino, dimethylamino, diethylamino, aminomethyl, 2-aminoethyl, pyrrolidin-1-yl, piperidino, morpholino, piperazin-1-yl, homopiperazin-1-yl, 4-methylpiperazin-1-yl, 4-methylhomopiperazin-1-yl, pyrrolidin-1-ylmethyl, piperidinomethyl, morpholinomethyl, piperazin-1-ylmethyl and 4-methylpiperazin-1-ylmethyl; and

(D) methylaminomethyl, ethylaminomethyl, dimethylaminomethyl, diethylaminomethyl, 2-hydroxyethylaminomethyl, 2-methoxyethylaminomethyl, 2-aminoethoxy, 3-aminopropoxy, 2-methylaminoethoxy, 2-ethylaminoethoxy, 3-methylaminopropoxy, 3-ethylaminopropoxy, 2-dimethylaminoethoxy, 2-diethylaminoethoxy, 3-dimethylaminopropoxy, 3-diethylaminopropoxy, 2-pyridylmethoxy, 2-(imidazol-1-yl)ethoxy, 3-(imidazol-1-yl)propoxy, piperidin-4-yloxy, 1-methylpiperidin-4-yloxy, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 2-(4-methylpiperazin-1-yl)ethoxy and 3-(4-methylpiperazin-1-yl)propoxy;

or a pharmaceutically-acceptable salt thereof.

A preferred group of novel compounds according to this aspect of the invention is an amide derivative of the Formula I

wherein m is 1, the R^1 group is selected from the substituents defined in paragraph (B) hereinafter and the R^1 group is located at the 3- or 4-position,

or m is 2, at least one R^1 group is selected from the substituents defined in paragraph (B) hereinafter and one R^1 group may be selected from the substituents defined in paragraph (A) hereinafter and the R^1 groups, which may be the same or different, are located at the 3- and 4-positions :-

(A) hydroxy, methyl, ethyl, methoxy, ethoxy, dimethylamino, diethylamino,

pyrrolidin-1-yl, piperidino, morpholino, piperazin-1-yl, 4-methylpiperazin-1-yl, pyrrolidin-1-ylmethyl, piperidinomethyl, morpholinomethyl, piperazin-1-ylmethyl and 4-methylpiperazin-1-ylmethyl; and

(B) dimethylaminomethyl, diethylaminomethyl, 2-dimethylaminoethoxy, 2-diethylaminoethoxy, 3-dimethylaminopropoxy, 3-diethylaminopropoxy, 2-pyridylmethoxy, piperidin-4-yloxy, 1-methylpiperidin-4-yloxy, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 2-(4-methylpiperazin-1-yl)ethoxy and 3-(4-methylpiperazin-1-yl)propoxy;

p is 0;

R^3 is methyl;

q is 0; and

R^4 is phenyl which is substituted at the 3-position with a substituent selected from dimethylamino, diethylamino, pyrrolidin-1-yl, piperidino, morpholino, piperazin-1-yl and 4-methylpiperazin-1-yl;

or a pharmaceutically-acceptable salt thereof.

A further preferred group of novel compounds according to this aspect of the invention is an amide derivative of the Formula I

wherein m is 1, the R^1 group is selected from the substituents defined in paragraph (B) hereinafter and the R^1 group is located at the 3- or 4-position,

or m is 2, at least one R^1 group is selected from the substituents defined in paragraph (B) hereinafter and is located at the 3- or 4-position and the other R^1 group is selected from the substituents defined in paragraphs (A) or (B) hereinafter :-

(A) hydroxy, methyl, ethyl, methoxy, ethoxy, dimethylamino, diethylamino, pyrrolidin-1-yl, piperidino, morpholino, piperazin-1-yl, 4-methylpiperazin-1-yl, pyrrolidin-1-ylmethyl, piperidinomethyl, morpholinomethyl, piperazin-1-ylmethyl and 4-methylpiperazin-1-ylmethyl; and

(B) dimethylaminomethyl, diethylaminomethyl, 2-dimethylaminoethoxy, 2-diethylaminoethoxy, 2-diisopropylaminoethoxy, 3-dimethylaminopropoxy, 3-diethylaminopropoxy, 2-(pyrrolidin-1-yl)ethoxy, 3-(pyrrolidin-1-yl)propoxy, 2-(N-methylpyrrolidin-2-yl)ethoxy, 2-piperidinoethoxy, 3-piperidinopropoxy,

2-morpholinoethoxy, 3-morpholinopropoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 2-(4-methylpiperazin-1-yl)ethoxy, 3-(4-methylpiperazin-1-yl)propoxy, 2-pyridylmethoxy, 2-methylthiazol-4-ylmethoxy, piperidin-4-yloxy, N-methylpiperidin-4-yloxy, N-methylhomopiperidin-4-yloxy, pyrrolidin-3-yloxy and N-methylpyrrolidin-3-yloxy;

p is 0;

R^3 is methyl;

q is 0; and

R^4 is phenyl which is substituted at the 3-position with a substituent selected from dimethylamino, diethylamino, pyrrolidin-1-yl, piperidino, morpholino, piperazin-1-yl, homopiperazin-1-yl, 4-methylpiperazin-1-yl and 4-methylhomopiperazin-1-yl and is optionally substituted with a further substituent selected from fluoro, chloro, cyano, methyl and trifluoromethyl;

or a pharmaceutically-acceptable salt thereof.

A further more preferred compound of this aspect of the invention is an amide derivative of the Formula I

wherein R^3 is methyl;

p is 0;

q is 0;

$(R^1)_m$ is 4-diethylaminomethyl, 3-(2-diethylaminoethoxy), 3-(2-pyrrolidin-1-ylethoxy), 4-methoxy-3-(2-pyrrolidin-1-ylethoxy) or 3-(piperidin-4-yloxy); and

R^4 is 3-morpholinophenyl;

or a pharmaceutically-acceptable salt thereof.

A further more preferred compound of this aspect of the invention is an amide derivative of the Formula I

wherein R^3 is methyl;

p is 0;

q is 0;

$(R^1)_m$ is 4-diethylaminomethyl, 3-(2-diethylaminoethoxy), 3-(2-diisopropylaminoethoxy), 3-(3-diethylaminopropoxy), 3-(2-pyrrolidin-1-ylethoxy), 3-[2-(N-methylpyrrolidin-2-yl)ethoxy], 3-(2-piperidinoethoxy), 3-(3-piperidinopropoxy), 4-[3-(4-methylpiperazin-

1-yl)propoxy], 4-methoxy-3-(2-pyrrolidin-1-ylethoxy), 4-methoxy-3-(2-piperidinoethoxy), 4-methoxy-3-(3-piperidinopropoxy), 4-methoxy-3-(2-diethylaminoethoxy), 4-methoxy-3-(3-diethylaminopropoxy), 4-methoxy-3-[2-(N-methylpyrrolidin-2-yl)ethoxy], 4-(2-pyridylmethoxy), 4-(2-methylthiazol-4-ylmethoxy), 3-piperidin-4-yloxy, 4-piperidin-4-yloxy, 3-(N-methylhomopiperidin-4-yloxy) and 3-pyrrolidin-3-yloxy; and R^4 is 3-pyrrolidin-1-ylphenyl, 3-piperidinophenyl, 3-morpholinophenyl, 3-fluoro-5-morpholinophenyl or 3-morpholino-5-trifluoromethylphenyl;
or a pharmaceutically-acceptable salt thereof.

Further particular preferred compounds of this aspect of the invention include, for example:-

N-[2-methyl-5-(3-morpholinobenzamido)phenyl]-3-piperidin-4-yloxybenzamide,
N-[2-methyl-5-(3-morpholinobenzamido)phenyl]-3-(2-pyrrolidin-1-ylethoxy)benzamide,
N-[2-methyl-5-(3-morpholinobenzamido)phenyl]-3-(2-diethylaminoethoxy)benzamide,
N-[2-methyl-5-(3-morpholinobenzamido)phenyl]-4-methoxy-3-(2-pyrrolidin-1-ylethoxy)benzamide and
N-[2-methyl-5-(3-morpholinobenzamido)phenyl]-4-diethylaminomethylbenzamide;
or the pharmaceutically-acceptable salts thereof.

Further particular preferred compounds of this aspect of the invention include, for example:-

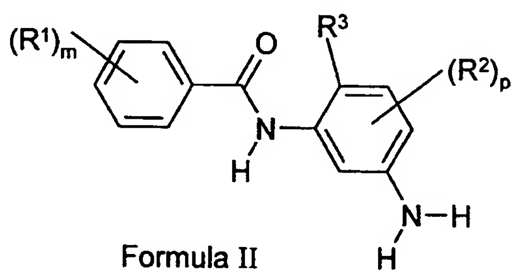
N-[2-methyl-5-(3-morpholinobenzamido)phenyl]-4-[3-(4-methylpiperazin-1-yl)propoxy]benzamide,
N-[2-methyl-5-(3-morpholinobenzamido)phenyl]-3-[2-(N-methylpyrrolidin-2-yl)ethoxy]benzamide,
N-[2-methyl-5-(3-pyrrolidin-1-ylbenzamido)phenyl]-3-piperidin-4-yloxybenzamide,
N-[2-methyl-5-(3-piperidinobenzamido)phenyl]-3-piperidin-4-yloxybenzamide,
N-[2-methyl-5-(3-morpholinobenzamido)phenyl]-3-(N-methylhomopiperidin-4-yloxy)benzamide,
N-[5-(3-fluoro-5-morpholinobenzamido)-2-methylphenyl]-3-piperidin-4-yloxybenzamide
N-[2-methyl-5-(3-morpholinobenzamido)phenyl]-4-(2-pyridylmethoxy)benzamide,
N-[5-(3-fluoro-5-morpholinobenzamido)-2-methylphenyl]-4-diethylaminomethylbenzamide
and N-[5-(3-fluoro-5-pyrrolidin-1-ylbenzamido)-2-methylphenyl]-

4-diethylaminomethylbenzamide;

or the pharmaceutically-acceptable salts thereof.

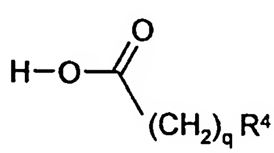
An amide derivative of the Formula I, or a pharmaceutically-acceptable salt or in-vivo-cleavable ester thereof, may be prepared by any process known to be applicable to the preparation of chemically-related compounds. Suitable processes are illustrated by, for example, those used in J. Med. Chem, 1996, 39, 3343-3356. Such processes, when used to prepare a novel amide derivative of the Formula I are provided as a further feature of the invention and are illustrated by the following representative process variants in which, unless otherwise stated, R^1, R^2, R^3, R^4, m, p and q have any of the meanings defined hereinbefore. Necessary starting materials may be obtained by standard procedures of organic chemistry. The preparation of such starting materials is described in conjunction with the following representative process variants and within the accompanying Examples. Alternatively necessary starting materials are obtainable by analogous procedures to those illustrated which are within the ordinary skill of an organic chemist.

(a) A compound of the Formula I, or a pharmaceutically-acceptable salt or in-vivo-cleavable ester thereof, may be prepared by reacting an aniline of the Formula II



Formula II

with an acid of the Formula III



Formula III

or an activated derivative thereof, under standard amide bond forming conditions, wherein variable groups are as hereinbefore defined and wherein any functional group is protected if necessary, and:

(i) removing any protecting groups;

(ii) optionally forming a pharmaceutically-acceptable salt or in-vivo-cleavable ester.

A suitable activated derivative of an acid of the Formula III is, for example, an acyl halide, for example an acyl chloride formed by the reaction of the acid and an inorganic acid chloride, for example thionyl chloride; a mixed anhydride, for example an anhydride formed by the reaction of the acid and a chloroformate such as isobutyl chloroformate; an active ester, for example an ester formed by the reaction of the acid and a phenol such as pentafluorophenol, an ester such as pentafluorophenyl trifluoroacetate or an alcohol such as N-hydroxybenzotriazole; an acyl azide, for example an azide formed by the reaction of the acid and an azide such as diphenylphosphoryl azide; an acyl cyanide, for example a cyanide formed by the reaction of an acid and a cyanide such as diethylphosphoryl cyanide; or the product of the reaction of the acid and a carbodiimide such as dicyclohexylcarbodiimide.

The reaction is preferably carried out in the presence of a suitable base such as, for example, an alkali or alkaline earth metal carbonate, alkoxide, hydroxide or hydride, for example sodium carbonate, potassium carbonate, caesium carbonate, sodium ethoxide, potassium butoxide, sodium hydroxide, potassium hydroxide, sodium hydride or potassium hydride, or an organometallic base such as an alkyl-lithium, for example n-butyl-lithium, or a dialkylamino-lithium, for example lithium di-isopropylamide, or, for example, an organic amine base such as, for example, pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, morpholine or diazabicyclo[5.4.0]undec-7-ene. The reaction is also preferably carried out in a suitable inert solvent or diluent, for example tetrahydrofuran, 1,2-dimethoxyethane, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidin-2-one, dimethylsulphoxide or acetone, and at a temperature in the range, for example, -78° to 150°C, conveniently at or near ambient temperature.

Typically a carbodiimide coupling reagent is used in the presence of an organic solvent (preferably an anhydrous polar aprotic organic solvent) at a non-extreme temperature, for example in the region -10 to 40°C, typically at ambient temperature of about 20°C.

Protecting groups may in general be chosen from any of the groups described in the literature or known to the skilled chemist as appropriate for the protection of the group in question and may be introduced by conventional methods. Protecting groups may be removed by any convenient method as described in the literature or known to the skilled chemist as

appropriate for the removal of the protecting group in question, such methods being chosen so as to effect removal of the protecting group with minimum disturbance of groups elsewhere in the molecule.

Specific examples of protecting groups are given below for the sake of convenience, in which "lower", as in, for example, lower alkyl, signifies that the group to which it is applied preferably has 1-4 carbon atoms. It will be understood that these examples are not exhaustive. Where specific examples of methods for the removal of protecting groups are given below these are similarly not exhaustive. The use of protecting groups and methods of deprotection not specifically mentioned is of course within the scope of the invention.

A carboxy protecting group may be the residue of an ester-forming aliphatic or arylaliphatic alcohol or of an ester-forming silanol (the said alcohol or silanol preferably containing 1-20 carbon atoms). Examples of carboxy protecting groups include straight or branched chain (1-12C)alkyl groups (for example isopropyl, tert-butyl); lower alkoxy lower alkyl groups (for example methoxymethyl, ethoxymethyl, isobutoxymethyl); lower aliphatic acyloxy lower alkyl groups, (for example acetoxymethyl, propionyloxymethyl, butyryloxymethyl, pivaloyloxymethyl); lower alkoxycarbonyloxy lower alkyl groups (for example 1-methoxycarbonyloxyethyl, 1-ethoxycarbonyloxyethyl); aryl lower alkyl groups (for example benzyl, p-methoxybenzyl, o-nitrobenzyl, p-nitrobenzyl, benzhydryl and phthalidyl); tri(lower alkyl)silyl groups (for example trimethylsilyl and tert-butyldimethylsilyl); tri(lower alkyl)silyl lower alkyl groups (for example trimethylsilylethyl); and (2-6C)alkenyl groups (for example allyl and vinylethyl). Methods particularly appropriate for the removal of carboxyl protecting groups include for example acid-, base-, metal- or enzymically-catalysed hydrolysis.

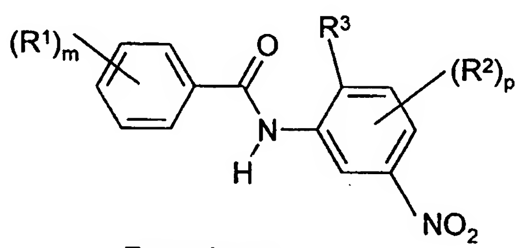
Examples of hydroxy protecting groups include lower alkyl groups (for example tert-butyl), lower alkenyl groups (for example allyl); lower alkanoyl groups (for example acetyl); lower alkoxycarbonyl groups (for example tert-butoxycarbonyl); lower alkenyloxycarbonyl groups (for example allyloxycarbonyl); aryl lower alkoxycarbonyl groups (for example benzoyloxycarbonyl, p-methoxybenzyloxycarbonyl, o-nitrobenzyloxycarbonyl, p-nitrobenzyloxycarbonyl); tri lower alkylsilyl (for example trimethylsilyl, tert-butyldimethylsilyl) and aryl lower alkyl (for example benzyl) groups.

Examples of amino protecting groups include formyl, aralkyl groups (for example benzyl and substituted benzyl, p-methoxybenzyl, nitrobenzyl and 2,4-dimethoxybenzyl, and triphenylmethyl); di-p-anisylmethyl and furylmethyl groups; lower alkoxycarbonyl (for example tert-butoxycarbonyl); lower alkenyloxycarbonyl (for example allyloxycarbonyl); aryl lower alkoxycarbonyl groups (for example benzyloxycarbonyl, p-methoxybenzyloxycarbonyl, o-nitrobenzyloxycarbonyl, p-nitrobenzyloxycarbonyl; trialkylsilyl (for example trimethylsilyl and tert-butyldimethylsilyl); alkylidene (for example methylidene); benzylidene and substituted benzylidene groups.

Methods appropriate for removal of hydroxy and amino protecting groups include, for example, acid-, base-, metal- or enzymically-catalysed hydrolysis for groups such as p-nitrobenzyloxycarbonyl, hydrogenation for groups such as benzyl and photolytically for groups such as o-nitrobenzyloxycarbonyl.

The reader is referred to Advanced Organic Chemistry, 4th Edition, by Jerry March, published by John Wiley & Sons 1992, for general guidance on reaction conditions and reagents. The reader is referred to Protective Groups in Organic Synthesis, 2nd Edition, by Green *et al.*, published by John Wiley & Sons for general guidance on protecting groups.

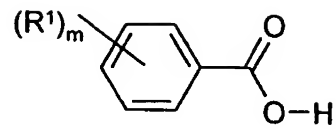
The aniline of Formula II may be prepared by reduction of the corresponding nitro compound of Formula IV.



Formula IV

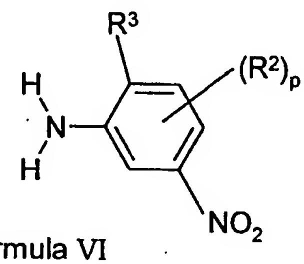
Typical reaction conditions include the use of ammonium formate in the presence of a catalyst (for example palladium-on-carbon) in the presence of an organic solvent (preferably a polar protic solvent), preferably with heating, for example to about 60°C. Any functional groups are protected and deprotected as necessary.

The compound of Formula IV may be prepared by reaction of an acid of Formula V, or an activated derivative thereof,



Formula V

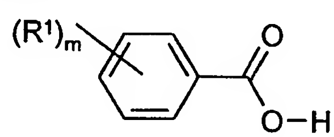
with an aniline of Formula VI under suitable amide bond forming conditions.



Formula VI

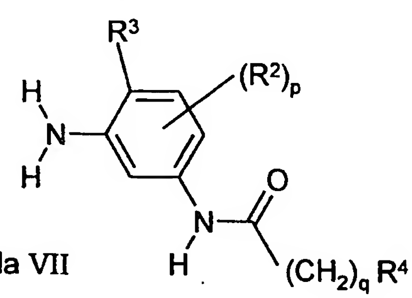
Typical conditions include activating the carboxy group of the compound of Formula V for example by treatment with a halo reagent (for example oxalyl chloride) to form an acyl halide in an organic solvent at ambient temperature, then reacting the activated compound with the aniline of Formula VI. Any functional groups are protected and deprotected as necessary.

(b) A compound of the Formula I, or a pharmaceutically-acceptable salt or in-vivo-cleavable ester thereof, may be prepared by reacting an acid of the Formula V



Formula V

or an activated derivative thereof as defined hereinbefore, with an aniline of the Formula VII



Formula VII

under standard amide bond forming conditions, wherein variable groups are as hereinbefore defined and wherein any functional group is protected, if necessary, and:

(i) removing any protecting groups;

(ii) optionally forming a pharmaceutically-acceptable salt or in-vivo-cleavable ester.

The aniline of Formula VII may be prepared by reduction of the corresponding nitro compound using convention procedures as defined hereinbefore or as illustrated in the Examples.

(c) A compound of the Formula I wherein R^1 or a substituent on R^4 is (1-6C)alkoxy or substituted (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylamino, di-[(1-6C)alkyl]amino or substituted (1-6C)alkylamino or heterocyclyloxy, may be prepared by the alkylation, conveniently in the presence of a suitable base as defined hereinbefore, of an amide derivative of the Formula I wherein R^1 or a substituent on R^4 is hydroxy, mercapto or amino as appropriate.

The reaction is preferably carried out in the presence of a suitable inert solvent or diluent, for example a halogenated solvent such as methylene chloride, chloroform or carbon tetrachloride, an ether such as tetrahydrofuran or 1,4-dioxan, an aromatic solvent such as toluene, or a dipolar aprotic solvent such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidin-2-one or dimethylsulphoxide. The reaction is conveniently carried out at a temperature in the range, for example, 10 to 150°C, preferably in the range 20 to 80°C.

A suitable alkylating agent is, for example, any agent known in the art for the alkylation of hydroxy to alkoxy or substituted alkoxy, or for the alkylation of mercapto to alkylthio, or for the alkylation of amino to alkylamino or substituted alkylamino, or for the alkylation of hydroxy to heterocyclyloxy, for example an alkyl or substituted alkyl halide or a heterocyclyl halide, for example a (1-6C)alkyl chloride, bromide or iodide or a substituted (1-6C)alkyl chloride, bromide or iodide or a heterocyclyl chloride, bromide or iodide, in the presence of a suitable base as defined hereinbefore.

(d) A compound of the Formula I wherein R^1 or a substituent on R^4 is (1-6C)alkanoylamino or substituted (2-6C)alkanoylamino may be prepared by the acylation of a compound of the Formula I wherein R^1 or a substituent on R^4 is amino.

A suitable acylating agent is, for example, any agent known in the art for the acylation of amino to acylamino, for example an acyl halide, for example a (1-6C)alkanoyl chloride or bromide, conveniently in the presence of a suitable base, as defined hereinbefore,

an alkanoic acid anhydride or mixed anhydride, for example a (1-6C)alkanoic acid anhydride such as acetic anhydride or the mixed anhydride formed by the reaction of an alkanoic acid and a (1-6C)alkoxycarbonyl halide, for example a (1-6C)alkoxycarbonyl chloride, in the presence of a suitable base as defined hereinbefore. In general the acylation is carried out in a suitable inert solvent or diluent as defined hereinbefore and at a temperature, in the range, for example, -30 to 120°C, conveniently at or near ambient temperature.

(e) A compound of the Formula I wherein R^1 or a substituent on R^4 is (1-6C)alkanesulphonylamino may be prepared by the reaction of a compound of the Formula I wherein R^1 or a substituent on R^4 is amino with a (1-6C)alkanesulphonic acid, or an activated derivative thereof.

A suitable activated derivative of a (1-6C)alkanesulphonic acid is, for example, an alkanesulphonyl halide, for example an alkanesulphonyl chloride formed by the reaction of the sulphonic acid and an inorganic acid chloride, for example thionyl chloride. The reaction is preferably carried out in the presence of a suitable base as defined hereinbefore, particularly pyridine, and in a suitable inert solvent or diluent as defined hereinbefore, particularly methylene chloride.

(f) A compound of the Formula I wherein R^1 or a substituent on R^4 is carboxy, carboxy-(1-6C)alkyl, carboxy-(1-6C)alkoxy, carboxy-(1-6C)alkylamino, N-(1-6C)alkyl-carboxy-(1-6C)alkylamino or carboxy-(2-6C)alkanoylamino may be prepared by the cleavage of a compound of the Formula I wherein R^1 or a substituent on R^4 is (1-6C)alkoxycarbonyl, (1-6C)alkoxycarbonyl-(1-6C)alkyl, (1-6C)alkoxycarbonyl-(1-6C)alkoxy, (1-6C)alkoxycarbonyl-(1-6C)alkylamino, N-(1-6C)alkyl-(1-6C)alkoxycarbonyl-(1-6C)alkylamino or (1-6C)alkoxycarbonyl-(2-6C)alkanoylamino as appropriate.

The cleavage reaction may conveniently be carried out by any of the many procedures known in the art for such a transformation. The reaction may be carried out, for example, by hydrolysis under acidic or basic conditions. A suitable base is, for example, an alkali metal, alkaline earth metal or ammonium carbonate or hydroxide, for example sodium carbonate, potassium carbonate, sodium hydroxide, potassium hydroxide or ammonium hydroxide. The reaction is preferably carried out in the presence of water and a suitable solvent or diluent such as methanol or ethanol. The reaction is conveniently carried out at a temperature in the range 10 to 150°C, preferably at or near ambient temperature.

(g) A compound of the Formula I wherein R^1 or a substituent on R^4 is amino-(1-6C)alkyl, heterocyclyl-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl, substituted (2-6C)alkylamino-(1-6C)alkyl or substituted N-(1-6C)alkyl-(2-6C)alkylamino-(1-6C)alkyl may be prepared by the reaction of a compound of the Formula I wherein R^1 or a substituent on R^4 is a group of the formula -(1-6C)alkylene-Z wherein Z is a displaceable group with an appropriate amine or heterocyclyl compound.

A suitable displaceable group Z is, for example, a halogeno group such as fluoro, chloro or bromo, a (1-6C)alkanesulphonyloxy group such as methanesulphonyloxy or an arylsulphonyloxy group such as 4-toluenesulphonyloxy.

The reaction is conveniently carried out in the presence of a suitable base as defined hereinbefore and in the presence of a suitable inert diluent or carrier as defined hereinbefore. The reaction is conveniently carried out at a temperature in the range 10 to 150°C, preferably at or near 50°C.

(h) A compound of the Formula I wherein R^1 or a substituent on R^4 is amino, heterocyclyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, substituted (1-6C)alkylamino, substituted N-(1-6C)alkyl-(1-6C)alkylamino, substituted (2-6C)alkylamino or substituted N-(1-6C)alkyl-(2-6C)alkylamino may be prepared by the reaction of a compound of the Formula I wherein R^1 or a substituent on R^4 is a displaceable group Z as defined hereinbefore with an appropriate amine or heterocyclyl compound.

The reaction is conveniently carried out in the presence of a suitable base as defined hereinbefore and in the presence of a suitable inert diluent or carrier as defined hereinbefore. The reaction is conveniently carried out at a temperature in the range 25 to 250°C, preferably at or near 150°C.

(i) A compound of the Formula I wherein R^1 or a substituent on R^4 is N-(1-6C)alkyl-(1-6C)alkanesulphonylamino may be prepared by the alkylation, conveniently in the presence of a suitable base as defined hereinbefore, of an amide derivative of the Formula I wherein R^1 or a substituent on R^4 is (1-6C)alkanesulphonylamino.

The reaction is conveniently carried out in the presence of a suitable inert diluent or carrier as defined hereinbefore and at a temperature in the range 10 to 150°C, preferably at or near ambient temperature.

(j) A compound of the Formula I wherein R^1 or a substituent on R^4 is a hydroxy-

heterocyclyl-(1-6C)alkoxy group (such as 2-hydroxy-3-piperidinopropoxy), a hydroxy-(1-6C)alkylamino-(2-6C)alkoxy group (such as 2-hydroxy-3-methylaminopropoxy) or a hydroxy-di-[(1-6C)alkyl]amino-(2-6C)alkoxy group (such as 3-dimethylamino-2-hydroxypropoxy or 3-[N-(3-dimethylaminopropyl)-N-methylamino]-2-hydroxypropoxy) may be prepared by the reaction of a compound of the Formula I wherein R^1 or a substituent on R^4 is a epoxy-substituted (1-6C)alkoxy group with a heterocyclyl compound or an appropriate amine.

The reaction is conveniently carried out in the presence of a suitable inert diluent or carrier as defined hereinbefore and at a temperature in the range 10 to 150°C, preferably at or near ambient temperature.

(k) A compound of the Formula I wherein R^1, R^2 or a substituent on R^4 is an amino group may be prepared by the reduction of a compound of the Formula I wherein R^1, R^2 or a substituent on R^4 is a nitro group.

Typical reaction conditions include the use of ammonium formate or hydrogen gas in the presence of a catalyst, for example a metallic catalyst such as palladium-on-carbon. Alternatively a dissolving metal reduction may be carried out, for example using iron in the presence of an acid, for example an inorganic or organic acid such as hydrochloric, hydrobromic, sulphuric or acetic acid. The reaction is conveniently carried out in the presence of an organic solvent (preferably a polar protic solvent) and preferably with heating, for example to about 60°C. Any functional groups are protected and deprotected as necessary.

The following biological assays and Examples serve to illustrate the present invention.

Biological Assays

The following assays can be used to measure the p38 kinase-inhibitory, the TNF-inhibitory and anti-arthritic effects of the compounds of the present invention:

In vitro enzyme assay

The ability of compounds of the invention to inhibit the enzyme p38 kinase was assessed. Activity of test compounds against each of the p38α and p38β isoforms of the enzyme was determined.

Human recombinant MKK6 (GenBank Accesion Number G1209672) was isolated from Image clone 45578 (Genomics, 1996, 33, 151) and utilised to produce protein in the form of a GST fusion protein in a pGEX vector using analogous procedures to those disclosed

by J. Han et al., Journal of Biological Chemistry, 1996, 271, 2886-2891. p38α (GenBank Accession Number G529039) and p38β (GenBank Accession Number G1469305) were isolated by PCR amplification of human lymphoblastoid cDNA (GenBank Accession Number GM1416) and human foetal brain cDNA [synthesised from mRNA (Clontech, catalogue no. 6525-1) using a Gibco superscript cDNA synthesis kit] respectively using oligonucleotides designed for the 5′ and 3′ ends of the human p38α and p38β genes using analogous procedures to those described by J.Han et al., Biochimica et Biophysica Acta, 1995, 1265, 224-227 and Y. Jiang et al., Journal of Biological Chemistry, 1996, 271, 17920-17926.

Both p38 protein isoforms were expressed in e coli in PET vectors. Human recombinant p38α and p38β isoforms were produced as 5′ c-myc, 6His tagged proteins. Both MKK6 and the p38 proteins were purified using standard protocols: the GST MKK6 was purified using a glutathione sepharose column and the p38 proteins were purified using nickel chelate columns.

The p38 enzymes were activated prior to use by incubation with MKK6 for 3 hours at 30°C. The unactivated coli-expressed MKK6 retained sufficient activity to fully activate both isoforms of p38. The activation incubate comprised p38α (10μl of 10mg/ml) or p38β (10μl of 5mg/ml) together with MKK6 (10μl of 1mg/ml), 'Kinase buffer' [100μl; pH 7.4 buffer comprising Tris (50mM), EGTA (0.1mM), sodium orthovanadate (0.1mM) and β-mercaptoethanol (0.1%)] and MgATP (30μl of 50mM $Mg(OCOCH_3)_2$ and 0.5mM ATP). This produced enough activated p38 enzyme for 3 Microtiter plates.

Test compounds were solubilised in DMSO and 10μl of a 1:10 diluted sample in 'Kinase Buffer' was added to a well in a Microtiter plate. For single dose testing, the compounds were tested at 10μM. 'Kinase Assay Mix' [30μl; comprising Myelin Basic Protein (Gibco BRL cat. no. 1322B-010; 1ml of a 3.33mg/ml solution in water), activated p38 enzyme (50μl) and 'Kinase Buffer' (2ml)] was then added followed by 'Labelled ATP' [10μl; comprising 50μM ATP, 0.1μCi ^{33}P ATP (Amersham International cat. no. BF1000) and 50mM $Mg(OCOCH_3)_2$]. The plates were incubated at room temperature with gentle agitation. Plates containing p38α were incubated for 90min and plates containing p38β were incubated for 45min. Incubation was stopped by the addition of 50μl of 20% trichloroacetic acid (TCA). The precipitated protein was phosphorylated by p38 kinase and test compounds were assessed for their ability to inhibit this phosphorylation. The plates were filtered using a

Canberra Packard Unifilter and washed with 2% TCA, dried overnight and counted on a Top Count scintillation counter.

Test compounds were tested initially at a single dose and active compounds were retested to allow IC_{50} values to be determined.

In vitro cell-based assays

(i) **PBMC**

The ability of compounds of this invention to inhibit TNFα production was assessed by using human peripheral blood mononuclear cells which synthesise and secrete TNFα when stimulated with lipopolysaccharide.

Peripheral blood mononuclear cells (PBMC) were isolated from heparinised (10units/ml heparin) human blood by density centrifugation (Lymphoprep™ ; Nycomed). Mononuclear cells were resuspended in culture medium [RPMI 1640 medium (Gibco) supplemented with 50 units/ml penicillin, 50μg/ml streptomycin, 2mM glutamine and 1% heat-inactivated human AB serum (Sigma H-1513)]. Compounds were solubilised in DMSO at a concentration of 50mM, diluted 1:100 in culture medium and subsequently serial dilutions were made in culture medium containing 1% DMSO. PBMCs (2.4×10^5 cells in 160μl culture medium) were incubated with 20μl of varying concentrations of test compound (triplicate cultures) or 20μl culture medium containing 1% DMSO (control wells) for 30 minutes at 37°C in a humidified (5%CO_2/95% air) incubator (Falcon 3072 ; 96 well flat-bottom tissue culture plates). 20μl lipopolysaccharide [LPS E.Coli 0111:B4 (Sigma L-4130), final concentration 10μg/ml] solubilised in culture medium was added to appropriate wells. 20μl culture medium was added to "medium alone" control wells. Six "LPS alone" and four "medium alone" controls were included on each 96 well plate. Varying concentrations of a known TNFα inhibitor were included in each test, i.e. an inhibitor of the PDE Type IV enzyme (for example see Semmler, J. Wachtel. H and Endres, S., Int. J. Immunopharmac. (1993), 15(3), 409-413) or an inhibitor of proTNFα convertase (for example, see McGeehan, G. M. et al. Nature (1994) 370, 558-561). Plates were incubated for 7 hours at 37°C (humidified incubator) after which 100μl of the supernatant was removed from each well and stored at -70°C (96 well round-bottom plates; Corning 25850). TNFα levels were determined in each sample using a human TNFα ELISA (see WO92/10190 and Current Protocols in Molecular Biology, vol 2 by Frederick M. Ausbel et al., John Wiley and Sons Inc.).

$$\% \text{ inhibition} = \frac{(\text{LPS alone - medium alone}) - (\text{test concentration - medium alone})}{(\text{LPS alone - medium alone})} \times 100$$

(ii) **Human Whole Blood**

The ability of the compounds of this invention to inhibit TNFα production was also assessed in a human whole blood assay. Human whole blood secretes TNFα when stimulated with LPS. This property of blood forms the basis of an assay which is used as a secondary test for compounds which profile as active in the PBMC test.

Heparinised (10 units/ml) human blood was obtained from volunteers. 160μl whole blood were added to 96 well round-bottom plates (Corning 25850). Compounds were solubilised and serially diluted in RPMI 1640 medium (Gibco) supplemented with 50 units/ml penicillin, 50μg/ml streptomycin and 2mM glutamine, as detailed above. 20μl of each test concentration was added to appropriate wells (triplicate cultures). 20μl of RPMI 1640 medium supplemented with antibiotics and glutamine was added to control wells. Plates were incubated for 30 minutes at 37°C (humidified incubator), prior to addition of 20μl LPS (final concentration 10μg/ml). RPMI 1640 medium was added to control wells. Six "LPS alone" and four "medium alone" controls were included on each plate. A known TNFα synthesis/secretion inhibitor was included in each test. Plates were incubated for 6 hours at 37°C (humidified incubator). Plates were centrifuged (2000rpm for 10 minutes) and 100μl plasma removed and stored at -70°C (Corning 25850 plates). TNFα levels were measured by ELISA (see WO92/10190 and Current Protocols in Molecular Biology, vol 2 by Frederick M. Ausbel et al., John Wiley and Sons Inc.). The paired antibodies that were used in the ELIZA were obtained from R&D Systems (catalogue nos. MAB610 anti-human TNFα coating antibody, BAF210 biotinylated anti-human TNFα detect antibody).

Ex vivo / In vivo assessment

The ability of the compounds of this invention as *ex vivo* TNFα inhibitors were assessed in the rat or mouse. Briefly, groups of male Wistar Alderley Park (AP) rats (180-210g) were dosed with compound (6 rats) or drug vehicle (10 rats) by the appropriate route, for example peroral (p.o.), intraperitoneal (i.p.) or subcutaneous (s.c.). Ninety minutes later rats were sacrificed using a rising concentration of CO_2 and bled out via the posterior vena cavae into 5 Units of sodium heparin/ml blood. Blood samples were immediately placed on

ice and centrifuged at 2000 rpm for 10 min at 4°C and the harvested plasmas frozen at -20°C for subsequent assay of their effect on TNFα production by LPS-stimulated human blood. The rat plasma samples were thawed and 175μl of each sample was added to a set format pattern in a 96 well round bottom plate (Corning 25850). 50μl of heparinized human blood was then added to each well, mixed and the plate was incubated for 30 min at 37°C (humidified incubator). LPS (25μl; final concentration10μg/ml) was added to the wells and incubation continued for a further 5.5 hours. Control wells were incubated with 25μl of medium alone. Plates were then centrifuged for 10 min at 2000 rpm and 200μl of the supernatants were transferred to a 96 well plate and frozen at -20°C for subsequent analysis of TNF concentration by ELISA.

Data analysis by dedicated software calculates for each compound/dose:

$$\% \text{ inhibition of TNF}\alpha = \frac{\text{Mean TNF}\alpha\text{ (Controls) - Mean TNF}\alpha\text{ (Treated)}}{\text{Mean TNF}\alpha\text{ (Controls)}} \times 100$$

Alternatively, mice could be used instead of rats in the above procedure.

Test as anti-arthritic agent

Activity of a compound as an anti-arthritic agent was tested as follows. Acid soluble native type II collagen was shown by Trentham et al. [1] to be arthritogenic in rats; it caused polyarthritis when administered in Freunds incomplete adjuvant. This is now known as collagen-induced arthritis (CIA) and similar conditions can be induced in mice and primates. Recent studies have shown that anti-TNF monoclonal antibodies [2] and TNF receptor-IgG fusion proteins [3] ameliorate established CIA indicating that TNF plays a key role in the pathophysiology of CIA. Moreover, the remarkable efficacy reported for anti-TNF monoclonal antibodies in recent rheumatoid arthritis clinical trials indicates that TNF plays a major role in this chronic inflammatory disease. Thus CIA in DBA/1 mice as described in references 2 and 3 is a tertiary model which can be used to demonstrate the anti-arthritic activity of a compound. Also see reference 4.

1. Trentham, D.E. *et al.*, (1977) J. Exp. Med., 146, 857.

2. Williams, R.O. *et al.*, (1992) Proc. Natl. Acad. Sci., 89, 9784.

3. Williams, R.O. *et al.*, (1995) Immunology, 84, 433.

4 Badger, M. B. *et al.*, (1996) The Journal of Pharmacology and Experimental Therapeutics, 279, 1453-1461.

Although the pharmacological properties of the compounds of the Formula I vary with structural change as expected, in general a compound of the Formula I gives over 30% inhibition in the PBMC test at concentrations up to 50μM. No physiologically unacceptable toxicity was observed at the effective dose for compounds tested of the present invention. By way of example :-

N-[5-(4-cyanobenzamido)-2-methylphenyl]-4-(2-methoxyethoxy)benzamide [Example 8] has an IC_{50} of approximately 0.1μM against p38α and an IC_{50} of approximately 3μM in the PBMC test; and

N-[2-methyl-5-(3-morpholinobenzamido)phenyl]-3-(2-pyrrolidin-1-ylethoxy)benzamide [Example 7, Compound No. 19] has an IC_{50} of approximately 0.1μM against p38α, an IC_{50} of approximately 1μM in the PBMC test and an IC_{50} of approximately 6μM in the Human Whole Blood test.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises an amide derivative of the Formula I, or a pharmaceutically-acceptable salt or in-vivo-cleavable ester thereof, as defined hereinbefore in association with a pharmaceutically-acceptable diluent or carrier.

The compositions of the invention may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions), for administration by inhalation (for example as a finely divided powder or a liquid aerosol), for administration by insufflation (for example as a finely divided powder) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous, intramuscular or intramuscular dosing or as a suppository for rectal dosing).

The compositions of the invention may be obtained by conventional procedures using conventional pharmaceutical excipients, well known in the art. Thus, compositions intended for oral use may contain, for example, one or more colouring, sweetening, flavouring and/or preservative agents.

The amount of active ingredient that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treated and the particular route of administration. For example, a formulation intended for oral

administration to humans will generally contain, for example, from 0.5 mg to 0.5 g of active agent compounded with an appropriate and convenient amount of excipients which may vary from about 5 to about 98 percent by weight of the total composition.

The size of the dose for therapeutic or prophylactic purposes of a compound of the Formula I will naturally vary according to the nature and severity of the conditions, the age and sex of the animal or patient and the route of administration, according to well known principles of medicine.

In using a compound of the Formula I for therapeutic or prophylactic purposes it will generally be administered so that a daily dose in the range, for example, 0.5 mg to 75 mg per kg body weight is received, given if required in divided doses. In general lower doses will be administered when a parenteral route is employed. Thus, for example, for intravenous administration, a dose in the range, for example, 0.5 mg to 30 mg per kg body weight will generally be used. Similarly, for administration by inhalation, a dose in the range, for example, 0.5 mg to 25 mg per kg body weight will be used. Oral administration is however preferred, particularly in tablet form. Typically, unit dosage forms will contain about 1 mg to 500 mg of a compound of this invention.

According to a further aspect of the invention there is provided an amide derivative of the Formula I, or a pharmaceutically-acceptable salt or in-vivo-cleavable ester thereof, as defined hereinbefore for use in a method of treatment of the human or animal body by therapy.

According to a further aspect of the invention there is provided the use of an amide derivative of the Formula I, or a pharmaceutically-acceptable salt or in-vivo-cleavable ester thereof, as defined hereinbefore in the manufacture of a medicament for use in the treatment of medical conditions mediated by cytokines.

In a further aspect the present invention provides a method of treating diseases or medical conditions mediated by cytokines which comprises administering to a warm-blooded animal an effective amount of a compound of the Formula I, or a pharmaceutically-acceptable salt or in-vivo-cleavable ester thereof.

In a further aspect the present invention provides the use of a compound of the Formula I, or a pharmaceutically-acceptable salt or in-vivo-cleavable ester thereof, in the manufacture of a medicament for use in the treatment of diseases or medical conditions

mediated by TNF, IL-1, IL-6 or IL-8.

In a further aspect the present invention provides a method of treating diseases or medical conditions mediated by TNF, IL-1, IL-6 or IL-8 which comprises administering to a warm-blooded animal an effective amount of a compound of the Formula I or a pharmaceutically-acceptable salt or in-vivo-cleavable ester thereof.

In a further aspect the present invention provides the use of a compound of the Formula I, or a pharmaceutically-acceptable salt or in-vivo-cleavable ester thereof in the manufacture of a medicament for use in the treatment of diseases or medical conditions mediated by TNF.

In a further aspect the present invention provides a method of treating diseases or medical conditions mediated by TNF which comprises administering to a warm-blooded animal an effective amount of a compound of the Formula I, or a pharmaceutically-acceptable salt or in-vivo-cleavable ester thereof.

In a further aspect the present invention provides the use of a compound of the Formula I, or a pharmaceutically-acceptable salt or in-vivo-cleavable ester thereof, in the manufacture of a medicament for use in inhibiting TNF, IL-1, IL-6 or IL-8.

In a further aspect the present invention provides a method of inhibiting TNF, IL-1, IL-6 or IL-8 which comprises administering to a warm-blooded animal an effective amount of a compound of the Formula I, or a pharmaceutically-acceptable salt or in-vivo-cleavable ester thereof.

In a further aspect the present invention provides the use of a compound of the Formula I, or a pharmaceutically-acceptable salt or in-vivo-cleavable ester thereof, in the manufacture of a medicament for use in inhibiting TNF.

In a further aspect the present invention provides a method of inhibiting TNF which comprises administering to a warm-blooded animal an effective amount of a compound of the Formula I, or a pharmaceutically-acceptable salt or in vivo-cleavable ester thereof.

In a further aspect the present invention provides the use of a compound of the Formula I, or a pharmaceutically-acceptable salt or in-vivo-cleavable ester thereof, in the manufacture of a medicament for use in the treatment of diseases or medical conditions mediated by p38 kinase.

In a further aspect the present invention provides a method of treating diseases or

medical conditions mediated by p38 kinase which comprises administering to a warm-blooded animal an effective amount of a compound of the Formula I, or a pharmaceutically-acceptable salt or in-vivo-cleavable ester thereof.

In a further aspect the present invention provides the use of a compound of the Formula I, or a pharmaceutically-acceptable salt or in-vivo-cleavable ester thereof, in the manufacture of a medicament for use in the production of a p38 kinase inhibitory effect.

In a further aspect the present invention provides a method of providing a p38 kinase inhibitory effect which comprises administering to a warm-blooded animal an effective amount of a compound of the Formula I, or a pharmaceutically-acceptable salt or in-vivo-cleavable ester thereof.

In a further aspect the present invention provides the use of a compound of the Formula I, or a pharmaceutically-acceptable salt or in-vivo- cleavable ester thereof, in the manufacture of a medicament for use in the treatment of rheumatoid arthritis, asthma, irritable bowel disease, multiple sclerosis, AIDS, septic shock, congestive heart failure, ischaemic heart disease or psoriasis.

In a further aspect the present invention provides a method of treating rheumatoid arthritis, asthma, irritable bowel disease, multiple sclerosis, AIDS, septic shock, congestive heart failure, ischaemic heart disease or psoriasis which comprises administering to a warm-blooded animal an effective amount of a compound of the Formula I, or a pharmaceutically-acceptable salt or in -vivo-cleavable ester thereof.

The compounds of this invention may be used in combination with other drugs and therapies used in the treatment of disease states which would benefit from the inhibition of cytokines, in particular TNF and IL-1. For example, the compounds of the Formula I could be used in combination with drugs and therapies used in the treatment of rheumatoid arthritis, asthma, irritable bowel disease, multiple sclerosis, AIDS, septic shock, congestive heart failure, ischaemic heart disease, psoriasis and the other disease states mentioned earlier in this specification.

For example, by virtue of their ability to inhibit cytokines, the compounds of the Formula I are of value in the treatment of certain inflammatory and non-inflammatory diseases which are currently treated with a cyclooxygenase-inhibitory non-steroidal anti-inflammatory drug (NSAID) such as indomethacin, ketorolac, acetylsalicyclic acid,

ibuprofen, sulindac, tolmetin and piroxicam. Co-administration of a compound of the Formula I with a NSAID can result in a reduction of the quantity of the latter agent needed to produce a therapeutic effect. Thereby the likelihood of adverse side-effects from the NSAID such as gastrointestinal effects are reduced. Thus according to a further feature of the invention there is provided a pharmaceutical composition which comprises a compound of the Formula I, or a pharmaceutically-acceptable salt or in-vivo-cleavable ester thereof, in conjunction or admixture with a cyclooxygenase inhibitory non-steroidal anti-inflammatory agent, and a pharmaceutically-acceptable diluent or carrier.

The compounds of the invention may also be used with anti-inflammatory agents such as an inhibitor of the enzyme 5-lipoxygenase.

The compounds of the Formula I may also be used in the treatment of conditions such as rheumatoid arthritis in combination with antiarthritic agents such as gold, methotrexate, steroids and penicillinamine, and in conditions such as osteoarthritis in combination with steroids.

The compounds of the present invention may also be administered in degradative diseases, for example osteoarthritis, with chondroprotective, anti-degradative and/or reparative agents such as Diacerhein, hyaluronic acid formulations such as Hyalan, Rumalon, Arteparon and glucosamine salts such as Antril.

The compounds of the Formula I may be be used in the treatment of asthma in combination with antiasthmatic agents such as bronchodilators and leukotriene antagonists.

If formulated as a fixed dose such combination products employ the compounds of this invention within the dosage range described herein and the other pharmaceutically-active agent within its approved dosage range. Sequential use is contemplated when a combination formulation is inappropriate.

Although the compounds of the Formula I are primarily of value as therapeutic agents for use in warm-blooded animals (including man), they are also useful whenever it is required to inhibit the effects of cytokines. Thus, they are useful as pharmacological standards for use in the development of new biological tests and in the search for new pharmacological agents.

The invention will now be illustrated in the following non-limiting Examples in which, unless otherwise stated:-

(i) operations were carried out at ambient temperature, *i.e.* in the range 17 to 25°C

and under an atmosphere of an inert gas such as argon unless otherwise stated;

(ii) evaporations were carried out by rotary evaporation in vacuo and work-up procedures were carried out after removal of residual solids by filtration;

(iii) column chromatography (by the flash procedure) and medium pressure liquid chromatography (MPLC) were performed on Merck Kieselgel silica (Art. 9385) or Merck Lichroprep RP-18 (Art. 9303) reversed-phase silica obtained from E. Merck, Darmstadt, Germany or high pressure liquid chromatography (HPLC) was performed on C18 reverse phase silica, for example on a Dynamax C-18 60Å preparative reversed-phase column;

(iv) yields are given for illustration only and are not necessarily the maximum attainable;

(v) in general, the end-products of the Formula I have satisfactory microanalyses and their structures were confirmed by nuclear magnetic resonance (NMR) and/or mass spectral techniques; fast-atom bombardment (FAB) mass spectral data were obtained using a Platform spectrometer and, where appropriate, either positive ion data or negative ion data were collected; NMR chemical shift values were measured on the delta scale [proton magnetic resonance spectra were determined using a Varian Gemini 2000 spectrometer operating at a field strength of 300MHz or a Bruker AM250 spectrometer operating at a field strength of 250MHz]; the following abbreviations have been used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad;

(vi) intermediates were not generally fully characterised and purity was assessed by thin layer chromatographic, HPLC, infra-red (IR) and/or NMR analysis;

(vii) melting points are uncorrected and were determined using a Mettler SP62 automatic melting point apparatus or an oil-bath apparatus; melting points for the end-products of the Formula I were determined after crystallisation from a conventional organic solvent such as ethanol, methanol, acetone, ether or hexane, alone or in admixture; and

(viii) the following abbreviations have been used:-

DMA	N,N-dimethylacetamide
DMF	N,N-dimethylformamide
DMSO	dimethylsulphoxide
THF	tetrahydrofuran

Example 1

N-[5-(3-methanesulphonylaminobenzamido)-2-methylphenyl]-3,4-dimethoxybenzamide

Methanesulphonyl chloride (0.25 g) was added to a stirred mixture of N-[5-(3-aminobenzamido)-2-methylphenyl]-3,4-dimethoxybenzamide (0.84 g), pyridine (0.5 ml) and methylene chloride (25 ml) and the mixture was stirred at ambient temperature for 48 hours. The mixture was washed with 2N hydrochloric acid and with water, dried ($MgSO_4$) and evaporated. The residue was triturated under diethyl ether and the resultant white solid was dried under vacuum at 60°C. There was thus obtained the title compound (0.85 g), m.p. >300°C; NMR Spectrum: ($DMSOd_6$) 2.18 (s, 3H), 3.03 (s, 3H), 3.82 (s, 6H), 7.06 (d, 1H), 7.23 (d, 1H), 7.4 (br d, 1H), 7.47 (t, 1H), 7.55 (br m, 2H), 7.63 (m, 1H), 7.66 (br d, 1H), 7.72 (d, 1H), 7.78 (d, 1H), 9.73 (br s, 1H), 9.91 (br s, 1H), 10.24 (br s, 1H); Mass Spectrum: M-H$^-$ 482.

The N-[5-(3-aminobenzamido)-2-methylphenyl]-3,4-dimethoxybenzamide used as starting material was prepared as follows :-

A solution of 3,4-dimethoxybenzoyl chloride (11.5 g) in methylene chloride (100 ml) was added dropwise to a stirred mixture of 2-methyl-5-nitroaniline (8.74 g), pyridine (18.6 ml) and methylene chloride (200 ml) and the mixture was stirred at ambient temperature for 18 hours. The mixture was washed with 2N hydrochloric acid and with water, dried ($MgSO_4$) and evaporated. The resultant solid was dried under vacuum at 60°C. There was thus obtained N-(2-methyl-5-nitrophenyl)-3,4-dimethoxybenzamide (15.9 g), m.p. >300°C; NMR Spectrum: ($CDCl_3$) 2.43 (s, 3H), 3.94 (m, 6H), 6.93 (m, 1H), 7.38 (m, 2H), 7.51 (m, 1H), 7.75 (br s, 1H), 7.94 (d, 1H), 8.89 (br m, 1H).

10% Palladium-on-carbon (4 g) was added to a stirred suspension of the material so obtained in methanol (1500 ml) and the mixture was stirred under an atmosphere of hydrogen gas. After cessation of hydrogen uptake, the catalyst was removed by filtration and the filtrate was evaporated. The residue was washed with diethyl ether and dried under vacuum at 60°C. There was thus obtained N-(5-amino-2-methylphenyl)-3,4-dimethoxybenzamide (11.3 g), m.p. 157-158°C; NMR Spectrum: ($CDCl_3$) 2.24 (s, 3H), 3.64 (br s, 2H), 3.95 (m, 6H), 6.44 (m, 1H), 6.93 (d, 1H), 6.98 (d, 1H), 7.38 (m, 1H), 7.54 (m, 2H), 7.6 (br s, 1H).

The material so obtained was reacted with 3-nitrobenzoyl chloride using an analogous procedure to that described in the first paragraph of the portion of this Example which is

concerned with the preparation of starting materials. There was thus obtained N-[2-methyl-5-(3-nitrobenzamido)phenyl]-3,4-dimethoxybenzamide, m.p. 232-233°C; NMR Spectrum: ($CDCl_3$) 2.19 (s, 3H), 3.83 (s, 6H), 7.07 (d, 1H), 7.24 (d, 1H), 7.61 (m, 3H), 7.83 (t, 2H), 8.45 (m, 2H), 8.79 (d, 1H), 9.76 (s, 1H), 10.55 (br s, 1H).

10% Palladium-on-carbon (0.13 g) was added to a stirred suspension of the material so obtained (1.27 g) in methanol (150 ml) and the mixture was stirred under an atmosphere of hydrogen gas. After cessation of hydrogen uptake the catalyst was removed by filtration and the filtrate was evaporated. The residue was washed with diethyl ether (50 ml) and dried under vacuum at 60°C. There was thus obtained N-[5-(3-aminobenzamido)-2-methylphenyl]-3,4-dimethoxybenzamide (1.02 g), m.p. 179-180°C; NMR Spectrum: ($DMSOd_6$) 2.15 (s, 3H), 3.82 (s, 6H), 5.25 (s, 2H), 6.72 (d, 1H), 7.05 (br m, 3H), 7.1 (t, 1H), 7.19 (d, 1H), 7.52 (m, 1H), 7.55 (d, 1H), 7.63 (m, 1H), 7.79 (d, 1H), 9.76 (br s, 1H), 10.02 (br s, 1H).

Example 2

N-[5-(4-chloromethylbenzamido)-2-methylphenyl]-3,4-dimethoxybenzamide

4-(Chloromethyl)benzoyl chloride (0.73 g) was added dropwise to a stirred mixture of N-(5-amino-2-methylphenyl)-3,4-dimethoxybenzamide (1 g), triethylamine (0.98 ml) and methylene chloride (80 ml) and the mixture was stirred at ambient temperature for 16 hours. A 1N hydrochloric acid solution (10 ml) was added and the resultant solution was stirred at ambient temperature for 1 hour. The resultant white solid was filtered off, washed with water and with diethyl ether, dried under vacuum at 40°C to give the title compound (1.35 g); NMR Spectrum: ($DMSOd_6$) 2.18 (s, 3H), 3.82 (s, 6H), 4.82 (s, 2H), 7.06 (d, 1H), 7.21 (d, 1H), 7.58 (m, 5H), 7.81 (s, 1H), 7.94 (d, 2H), 9.76 (s, 1H), 10.23 (s, 1H);
Mass Spectrum: $M+H^+$ 439.

Example 3

N-{5-[4-(3-chloropropoxy)benzamido]-2-methylphenyl}-3,4-dimethoxybenzamide

Oxalyl chloride (2.13 g) was added to a stirred mixture of 4-(3-chloropropoxy)-benzoic acid (3 g), DMF (3 drops) and methylene chloride (150 ml) and the mixture was stirred at ambient temperature for 3 hours. The solvent was evaporated. The residue was dissolved in methylene chloride (80 ml) and added dropwise to a stirred mixture of

N-(5-amino-2-methylphenyl)-3,4-dimethoxybenzamide (3.33 g), pyridine (3.77 ml) and methylene chloride (120 ml). The resultant mixture was stirred at ambient temperature for 18 hours. The mixture was washed in turn with 2N hydrochloric acid, water, a saturated aqueous sodium bicarbonate solution and water. The organic phase was dried ($MgSO_4$) and evaporated. The residue was triturated under diethyl ether and the resultant white solid was dried under vacuum at 60°C to give the title compound (5.05 g), m.p. 186-187°C; NMR Spectrum: ($DMSOd_6$) 2.18 (m, 5H), 3.8 (t, 2H), 3.83 (s, 6H), 4.17 (t, 2H), 7.07 (m, 3H), 7.21 (d, 1H), 7.55 (m, 1H), 7.63 (m, 1H), 7.8 (d, 1H); 7.95 (d, 2H), 9.74 (br s, 1H), 10.05 (br s, 1H); Mass Spectrum: $M+H^+$ 483.

Example 4

N-{5-[4-(2-pyrrolidin-1-ylethoxy)benzamido]-2-methylphenyl}-3,4-dimethoxybenzamide

N-(2-Chloroethyl)pyrrolidine hydrochloride (0.13 g) was added to a stirred mixture of N-[5-(4-hydroxybenzamido)-2-methylphenyl]-3,4-dimethoxybenzamide (0.25 g), potassium carbonate (0.26 g) and DMA (5 ml) and the resultant mixture was stirred and heated to 60°C for 1 week. The mixture was allowed to cool to ambient temperature and poured into water (125ml). The resultant precipitate was isolated, washed with water and with diethyl ether and dried under vacuum at 60°C. There was thus obtained the title compound (0.208 g), m.p. 165-166°C; NMR Spectrum: ($DMSOd_6$) 1.17 (m, 4H), 2.17 (s, 3H), 2.49 (br m, 4H), 2.79 (t, 2H), 3.83 (s, 6H), 4.13 (t, 2H), 7.05 (t, 3H), 7.2 (d, 1H), 7.55 (m, 2H), 7.625 (m, 1H), 7.81 (d, 1H); 7.94 (d, 2H), 9.74 (br s, 1H), 10.03 (br s, 1H); Mass Spectrum: $(M-H)^-$ 502.

The N-[5-(4-hydroxybenzamido)-2-methylphenyl]-3,4-dimethoxybenzamide used as starting material was prepared as follows :-

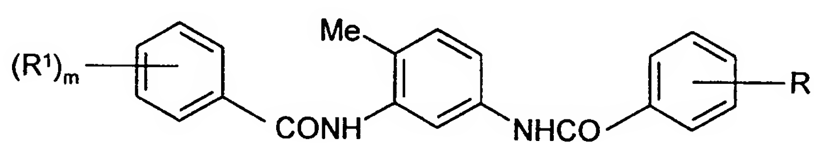
N-(5-Amino-2-methylphenyl)-3,4-dimethoxybenzamide was reacted with 4-benzyloxybenzoyl chloride using an analogous procedure to that described in the first paragraph of the portion of Example 1 which is concerned with the preparation of starting materials. There was thus obtained N-[5-(4-benzyloxybenzamido)-2-methylphenyl]-3,4-dimethoxybenzamide, m.p. 186-187°C; NMR Spectrum: ($CDCl_3$) 2.17 (s, 3H), 3.83 (s, 6H), 5.18 (s, 2H), 7.07 (d, 1H), 7.13 (d, 2H), 7.2 (d, 1H), 7.37 (m, 3H), 7.45 (m, 2H), 7.55 (m, 2H), 7.63 (m, 1H) , 7.8 (d, 1H), 7.94 (d, 2H), 9.74 (br s, 1H), 10.04 (br s, 1H).

10% Palladium-on-carbon (0.5 g) was added to a stirred suspension of N-[5-(4-benzyloxybenzamido)-2-methylphenyl]-3,4-dimethoxybenzamide (3.97 g) in methanol (500 ml) and the mixture was stirred under an atmosphere of hydrogen gas. After cessation of hydrogen uptake, the catalyst was removed by filtration and the filtrate was evaporated. The residue was washed with diethyl ether and dried under vacuum at 60°C. There was thus obtained the required starting material (2.93 g), m.p. 258-259°C; NMR Spectrum: ($DMSOd_6$) 2.17 (s, 3H), 3.83 (s, 6H), 6.84 (d, 2H), 7.05 (d, 1H), 7.19 (d, 1H), 7.54 (m, 2H), 7.65 (d, 1H), 7.78 (d, 1H), 7.84 (d, 2H), 9.74 (br s, 1H), 9.93 (br s, 1H).

Example 5

Using an analogous procedure to that described in Example 4, the appropriate phenol was reacted with the appropriate alkyl halide to give the compounds described in Table I.

Table I



No.	$(R^1)_m$	R	Note
1	3,4-dimethoxy	4-(2-diethylaminoethoxy)	a
2	3,4-dimethoxy	3-(2-morpholinoethoxy)	b
3	3,4-dimethoxy	4-(3-morpholinopropoxy)	c
4	3,4-dimethoxy	4-tert-butoxycarbonylmethoxy	d
5	3,4-dimethoxy	3-tert-butoxycarbonylmethoxy	e
6	3,4-dimethoxy	3-(3-morpholinopropoxy)	f
7	3,4-dimethoxy	2-tert-butoxycarbonylmethoxy	g
8	3,4-dimethoxy	2-(2-pyridylmethoxy)	h
9	3,4-dimethoxy	3-(2-pyridylmethoxy)	i
10	3,4-dimethoxy	2,3-di-(2-pyridylmethoxy)	j

Notes

a) The product gave the following data : NMR ($DMSOd_6$) 0.96 (t, 6H), 2.18 (s, 3H), 2.53 (m, 4H), 2.76 (t, 2H), 3.83 (s, 6H), 4.08 (t, 2H), 7.04 (m, 3H), 7.2 (d, 1H), 7.55 (m, 2H), 7.63 (m, 1H), 7.79 (d, 1H), 7.94 (d, 2H), 9.74 (br s,1H), 10.03 (br s, 1H); Mass M+H 506.

b) The product gave the following data : NMR ($DMSOd_6$) 2.18 (s, 3H), 2.47 (t, 4H), 2.7 (t, 2H), 3.56 (t, 4H), 3.82 (s, 6H), 4.15 (t, 2H), 7.06 (d, 1H), 7.13 (m, 1H), 7.22 (d, 1H), 7.42 (t, 1H), 7.51 (d, 1H), 7.56 (br m, 3H), 7.63 (m, 1H), 7.8 (d, 1H), 9.75 (br s, 1H), 10.15 (br s, 1H); Mass M+H 520.

The N-[5-(3-hydroxybenzamido)-2-methylphenyl]-3,4-dimethoxybenzamide which was used as a starting material was prepared as follows. N-(5-Amino-2-methylphenyl)-3,4-dimethoxybenzamide was reacted with 3-benzyloxybenzoyl chloride using an analogous procedure to that described in the first paragraph of the portion of Example 1 which is concerned with the preparation of starting materials. There was thus obtained N-[5-(3-benzyloxybenzamido)-2-methylphenyl]-3,4-dimethoxybenzamide, m.p. 208-209°C; NMR: ($CDCl_3$) 2.21 (s, 3H), 3.83 (s, 6H), 5.18 (s, 2H), 7.06 (d, 1H), 7.21 (m, 2H), 7.4 (m, 5H), 7.55 (m, 3H), 7.62 (m, 1H), 7.8 (d, 1H), 9.77 (br s, 1H), 10.17 (br s, 1H).

The benzyloxy group was cleaved by hydrogenolysis using an analogous procedure to that described in the last paragraph of the portion of Example 4 which is concerned with the preparation of starting materials. There was thus obtained the required starting material, m.p. 182-183°C; NMR: ($CDCl_3$) 2.17 (s, 3H), 3.83 (s, 6H), 6.95 (m, 1H), 7.06 (d, 1H), 7.22 (d, 1H), 7.32 (m, 2H), 7.36 (d, 1H), 7.55 (m, 2H), 7.63 (m, 1H), 7.82 (d, 1H), 9.68 (br s, 2H), 9.75 (br s, 1H), 10.13 (br s, 1H).

c) The standard procedure was adapted to the following :-

Morpholine (0.27 g) and sodium iodide (0.33 g) were added in turn to a stirred solution of N-[5-(4-(3-chloropropoxy)benzamido)-2-methylphenyl]-3,4-dimethoxybenzamide (0.5 g) in acetone (15 ml) and the mixture was stirred and heated to reflux for 1 week. The mixture was evaporated and the residue was partitioned between methylene chloride and water. The organic phase was washed with water, dried ($MgSO_4$) and evaporated. The residual solid was triturated under diethyl ether and the

resultant solid was dried under vacuum at 60°C. There was thus obtained N-{2-methyl-5-[4-(3-morpholinopropoxy)benzamido]phenyl}-3,4-dimethoxybenzamide (0.47 g), m.p. 148-149°C; NMR ($DMSOd_6$) 1.87 (m, 2H), 2.17 (s, 3H), 2.38 (br m, 6H), 3.55 (br m, 4H), 3.82 (s, 6H), 4.07 (t, 2H), 7.06 (m, 3H), 7.2 (d, 1H), 7.55 (d, 2H), 7.63 (m, 1H), 7.8 (d, 1H), 7.94 (d, 2H), 9.76 (br s, 1H), 10.04 (br s, 1H); Mass M+H 534.

d) The phenol was reacted with tert-butyl bromoacetate. The product gave the following data : m.p. 193-194°C; NMR ($DMSOd_6$) 1.43 (s, 9H), 2.18 (s, 3H), 3.83 (s, 6H), 4.74 (s, 2H), 7.01 (d, 2H), 7.06 (d, 1H), 7.21 (d, 1H), 7.55 (m, 2H), 7.62 (m, 1H), 7.8 (d, 1H), 7.93 (d, 2H), 9.75 (br s, 1H), 10.06 (br s, 1H); Mass M+H 521.

e) The phenol was reacted with tert-butyl bromoacetate. The product gave the following data : m.p. 182-183°C; NMR ($DMSOd_6$) 1.43 (s, 9H), 2.18 (s, 3H), 3.83 (s, 6H), 4.75 (s, 2H), 7.06 (d, 2H), 7.12 (m, 1H), 7.23 (d, 1H), 7.42 (t, 1H), 7.44 (br s, 1H), 7.58 (br m, 1H), 7.63 (m, 1H), 7.8 (d, 1H), 9.77 (br s, 1H), 10.17 (br s, 1H); Mass M+H 521.

f) The reactants were heated to 90°C for 18 hours. The product gave the following data : NMR ($DMSOd_6$) 2.18 (s, 3H), 2.23 (m, 2H), 3.04 (m, 2H), 3.24 (m, 2H), 3.44 (m, 2H), 3.82 (m, 8H), 3.92 (m, 2H), 4.15 (t, 2H), 7.06 (d, 1H), 7.14 (m, 1H), 7.22 (m, 1H), 7.43 (t, 1H), 7.56 (m, 5H); 7.83 (d, 2H), 9.79 (br s, 1H), 10.3 (br s, 1H); Mass M+H 534.

g) The phenol was reacted with tert-butyl bromoacetate. The product gave the following data : m.p. 156-157°C; NMR ($DMSOd_6$) 1.43 (s, 1H), 2.18 (s, 3H), 3.83 (s, 6H), 4.89 (s, 2H), 7.06 (d, 1H), 7.13 (m, 2H), 7.24 (d, 1H), 7.49 (t, 1H), 7.3 (m, 2H), 7.47 (m, 2H), 7.57 (m, 2H), 7.63 (m, 1H), 7.89 (d, 2H), 9.76 (br s, 1H), 10.39 (br s, 1H); Mass M+H 521.

The N-[5-(2-hydroxybenzamido)-2-methylphenyl]-3,4-dimethoxybenzamide which was used as a starting material was prepared as follows :-

Oxalyl chloride (1.34 g) was added to a stirred mixture of 2-benzyloxybenzoic acid (2 g), DMF (3 drops) and methylene chloride (60 ml) and the resultant solution was stirred at ambient temperature for 3 hours. The solvent was evaporated and the residue was dissolved in methylene chloride (15 ml) and added dropwise to a stirred mixture of N-(5-amino-2-methylphenyl)-3,4-dimethoxybenzamide (2.09 g), pyridine (2.36 ml) and methylene chloride (45 ml). The mixture was stirred at ambient temperature for 72 hours. The resultant precipitate was isolated, washed in turn with methylene chloride

and diethyl ether and dried under vacuum at 60°C. There was thus obtained N-[5-(2-benzyloxybenzamido)-2-methylphenyl]-3,4-dimethoxybenzamide (2.62 g), m.p. 215-216°C; NMR: ($DMSOd_6$) 2.13 (s, 3H), 3.83 (s, 6H), 5.24 (s, 2H), 7.11 (m, 3H), 7.26 (m, 3H), 7.52 (m, 4H), 7.63 (m, 2H), 7.71 (m, 1H), 7.86 (t, 2H), 9.73 (br s, 1H), 10.13 (d, 1H); Mass: M+H 497.

10% Palladium-on-carbon (0.5 g) was added to a stirred mixture of the material so obtained (2.44 g) and methanol (300 ml) and the resultant mixture was stirred under one atmosphere pressure of hydrogen. After cessation of hydrogen uptake, the catalyst was removed by filtration and the filtrate was evaporated. The resultant solid was dried under vacuum at 60°C. There was thus obtained the required starting material (1.85 g). NMR: ($DMSOd_6$) 2.19 (s, 3H), 3.82 (s, 6H), 6.94 (m, 2H), 7.06 (d, 1H), 7.24 (d, 1H), 7.42 (t, 1H), 7.47 (m, 1H), 7.53 (d, 1H), 7.62 (m, 2H), 7.76 (d, 1H), 7.96 (m, 1H), 9.75 (br s, 1H), 10.35 (br s, 1H), 11.83 (br s, 1H); Mass: M-H 405.

h) The phenol was reacted with 2-chloromethylpyridine, the reactants being heated to 60°C for 18 hours. The product gave the following data : NMR ($DMSOd_6$) 2.18 (s, 3H), 3.83 (s, 6H), 5.4 (s, 2H), 7.08 (d, 1H), 7.1 (m, 1H), 7.23 (d, 1H), 7.43 (t, 1H), 7.3 (m, 2H), 7.47 (m, 2H), 7.58 (m, 2H), 7.64 (m, 1H), 7.75 (d, 1H), 7.81 (m, 2H), 8.6 (d, 1H), 9.78 (br s, 1H), 10.56 (br s, 1H); Mass M+H 498.

i) The phenol was reacted with 2-chloromethylpyridine, the reactants being heated to 70°C for 18 hours. The product gave the following data : m.p. 185-186°C; NMR ($DMSOd_6$) 2.18 (s, 3H), 3.82 (s, 6H), 5.25 (s, 2H), 7.05 (d, 1H), 7.23 (m, 2H), 7.34 (m, 1H), 7.43 (t, 1H), 7.52 (m, 4H), 7.62 (m, 2H), 7.8 (br s, 1H), 7.84 (m, 1H), 8.57 (d, 1H), 9.73 (br s, 1H), 10.17 (br s, 1H); Mass M+H 498.

j) The product gave the following data : NMR ($DMSOd_6$) 2.15 (s, 3H), 3.83 (s, 6H), 5.28 (s, 4H), 7.07 (d, 1H), 7.49 (m, 14H), 7.55 (m, 2H), 8.4 (d, 1H), 8.58 (d, 1H), 9.75 (br s, 1H), 10.55 (br s, 1H); Mass M+H 605.

The N-[5-(2,3-dihydroxybenzamido)-2-methylphenyl]-3,4-dimethoxybenzamide which was used as a starting material was prepared as follows :-

N-(5-Amino-2-methylphenyl)-3,4-dimethoxybenzamide was reacted with 2,3-dibenzyloxybenzoyl chloride using an analogous procedure to that described in the first paragraph of the portion of Example 1 which is concerned with the preparation of

starting materials. There was thus obtained N-[5-(2,3-dibenzyloxybenzamido)-2-methylphenyl]-3,4-dimethoxybenzamide, m.p. 166-167°C; NMR: ($DMSOd_6$) 2.16 (s, 3H), 3.82 (s, 6H), 5.1 (s, 2H), 5.23 (s, 2H), 7.05 (d, 1H), 7.17 (m, 3H), 7.36 (m, 7H), 7.52 (d, 2H), 7.56 (d, 1H), 7.63 (m, 1H), 7.69 (d, 1H), 9.75 (br s, 1H), 10.46 (br s, 1H).

10% palladium-on-carbon (0.5 g) was added to a solution of the material so obtained (2.6 g) in methanol (300 ml) and the mixture was stirred under an atmosphere of hydrogen. After cessation of hydrogen uptake, the catalyst was removed by filtration and the filtrate was evaporated. The residue was triturated under diethyl ether. The resultant solid was isolated and dried under vacuum at 60°C. There was thus obtained the required starting material (1.68 g), m.p. 210-211°C; NMR: ($DMSOd_6$) 2.19 (s, 3H), 3.84 (s, 6H), 6.33 (t, 1H), 6.75 (d, 1H), 6.95 (d, 1H), 7.06 (d, 1H), 7.25 (d, 1H), 7.47 (m, 2H), 7.58 (d, 1H), 7.64 (m, 1H), 9.77 (br s, 1H), 10.38 (br s, 1H).

Example 6

N-[5-(3-dimethylaminobenzamido)-2-methylphenyl]-4-(3-morpholinopropoxy)-benzamide

4-(3-Chloropropyl)morpholine (0.1 g) was added to a stirred mixture of N-[5-(3-dimethylaminobenzamido)-2-methylphenyl]-4-hydroxybenzamide (0.195 g), potassium carbonate (0.21 g) and DMA (5 ml). The mixture was then heated to 60°C for 36 hours. The mixture was poured into water (150 ml) and the resultant solid was collected, washed with water and with diethyl ether. The product was dried under vacuum. There was thus obtained the title compound (0.203 g) as a colourless solid; NMR Spectrum: ($DMSOd_6$) 1.88 (m, 2H), 2.18 (s, 3H), 2.36 (t, 4H), 2.41 (t, 2H), 2.96 (s, 6H), 3.58 (t, 4H), 4.08 (t, 2H), 6.9 (m, 1H), 7.01 (d, 2H), 7.19 (m, 3H), 7.26 (t, 1H), 7.58 (d, 1H), 7.78 (s, 1H), 7.98 (d, 2H), 9.72 (s, 1H), 10.08 (s, 1H); Mass Spectrum: $M+H^+$ 517.

The N-[5-(3-dimethylaminobenzamido)-2-methylphenyl]-4-hydroxybenzamide used as starting material was prepared as follows :-

Oxalyl chloride (0.5 ml) was added slowly to a stirred mixture of 4-acetoxybenzoic acid (1.09 g), methylene chloride (30 ml) and DMF (one drop) and the mixture was stirred at ambient temperature for 2 hours. A solution of 2-methyl-5-nitroaniline (0.76 g) and pyridine (2 ml) in methylene chloride was added over 15 minutes and the mixture was stirred for a

further 2 hours. The reaction mixture washed with a 5% aqueous acetic acid solution, with water and with a 5% aqueous sodium bicarbonate solution. The organic extract was dried ($MgSO_4$) and evaporated. The residue was recrystallised from ethyl acetate to give N-(2-methyl-5-nitrophenyl)-4-acetoxybenzamide (0.8 g), m.p. 207-208°C; NMR Spectrum: ($DMSOd_6$) 2.3 (s, 3H), 7.31 (d, 2H), 7.56 (d, 1H), 8.02 (m, 3H), 8.47 (d, 1H), 10.12 (s, 1H).

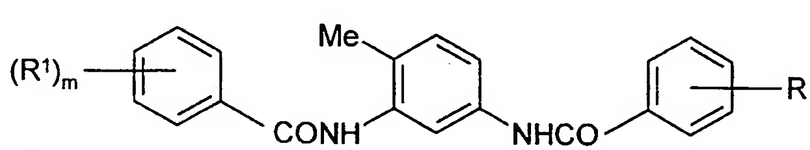
A mixture of a portion (0.5 g) of the material so obtained, ammonium formate (1 g), 10% palladium-on-carbon (0.25 g) and methanol (10 ml) was stirred and heated to 60°C for 2 hours. The reaction mixture was cooled and filtered and the filtrate was evaporated. The residue was triturated under water. The crude product was filtered from the aqueous solution and crystallised from methanol to give N-(5-amino-2-methylphenyl)-4-hydroxybenzamide (0.14 g), m.p. 277-278°C; NMR Spectrum: ($DMSOd_6$) 2.03 (s, 3H), 4.85 (s, 2H), 6.39 (m, 1H), 6.61(d, 1H), 6.85 (m, 3H), 7.82 (d, 2H), 9.3 (s, 1H), 9.96 (s, 1H).

4-Dimethylaminopyridine (0.13 g) was added to a mixture a portion (0.085 g) of the material so obtained, 3-dimethylaminobenzoic acid (0.089 g), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.103 g), methylene chloride (3 ml) and DMF (0.5 ml). The reaction mixture was stirred at ambient temperature for 18 hours. The mixture was evaporated and the residue was purified by column chromatography on silica eluting in turn with 50%, 60% and 70% ethyl acetate in isohexane. There was thus obtained N-[5-(3-dimethylaminobenzamido)-2-methylphenyl]-4-hydroxybenzamide (0.017 g); NMR Spectrum: ($DMSOd_6$) 2.17 (s, 3H), 2.96 (s, 6H), 6.80-6.95 (m, 3H), 7.15-7.35 (m, 4H), 7.58 (m, 1H), 7.79 (d, 1H), 7.87 (d, 2H), 9.62 (s, 1H), 9.95 (s, 1H), 10.1 (s, 1H).

Example 7

Using an analogous procedure to that described in Example 6, the appropriate phenol was reacted with the appropriate alkyl chloride to give the compounds described in Table II.

Table II



No.	$(R^1)_m$	R	Note
1	3-methoxy-4-(3-morpholinopropoxy)	3-dimethylamino	a
2	3-[2-(pyrrolidin-1-yl)ethoxy]	3-dimethylamino	b
3	3-(2-morpholinoethoxy)	3-dimethylamino	c
4	4-(2-morpholinoethoxy)	3-dimethylamino	d
5	3-(3-morpholinopropoxy)	3-dimethylamino	e
6	3-methoxy-4-(2-morpholinoethoxy)	3-dimethylamino	f
7	4-methoxy-3-(2-piperidinoethoxy)	3-dimethylamino	g
8	4-methoxy-3-[2-(pyrrolidin-1-yl)ethoxy]	3-dimethylamino	h
9	4-methoxy-3-(3-morpholinopropoxy)	3-dimethylamino	i
10	4-methoxy-3-(2-morpholinoethoxy)	3-dimethylamino	j
11	4-(2-pyridylmethoxy)	3-dimethylamino	k
12	3-(2-pyridylmethoxy)	3-dimethylamino	l
13	4-(2-methoxyethoxy)	3-dimethylamino	m
14	2-[2-(pyrrolidin-1-yl)ethoxy]	3-dimethylamino	n
15	4-[2-(pyrrolidin-1-yl)ethoxy]	3-dimethylamino	o
16	3-methoxy-4-[2-(pyrrolidin-1-yl)ethoxy]	3-dimethylamino	p
17	3-methoxy-4-(2-pyridylmethoxy)	3-dimethylamino	q
18	3-methoxy-4-(tert-butoxycarbonylmethoxy)	3-dimethylamino	r
19	3-[2-(pyrrolidin-1-yl)ethoxy]	3-morpholino	s
20	3-(2-piperidinoethoxy)	3-morpholino	t
21	3-(2-morpholinoethoxy)	3-morpholino	u
22	3-(2-diethylaminoethoxy)	3-morpholino	v
23	3-(2-pyridylmethoxy)	3-morpholino	w
24	4-methoxy-3-[2-(pyrrolidin-1-yl)ethoxy]	3-morpholino	x
25	4-methoxy-3-(2-morpholinoethoxy)	3-morpholino	y
26	4-methoxy-3-(2-pyridylmethoxy)	3-morpholino	z
27	3-(tert-butoxycarbonylmethoxy)	3-dimethylamino	aa
28	3-(3-piperidinopropoxy)	3-morpholino	bb
29	3-(3-morpholinopropoxy)	3-morpholino	cc

30	3-(2-diisopropylaminoethoxy)	3-morpholino	dd
31	3-(3-diethylaminopropoxy)	3-morpholino	ee
32	3-[2-(N-methylpyrrolidin-2-yl)ethoxy]	3-morpholino	ff
33	3-(3-pyridylmethoxy)	3-morpholino	gg
34	3-(4-pyridylmethoxy)	3-morpholino	hh
35	3-(2-methylthiazol-4-ylmethoxy)	3-morpholino	ii
36	3-(N-methylpiperidin-3-ylmethoxy)	3-morpholino	jj
37	4-(2-morpholinoethoxy)	3-morpholino	kk
38	4-(3-morpholinopropoxy)	3-morpholino	ll
39	4-[2-(pyrrolidin-1-yl)ethoxy]	3-morpholino	mm
40	4-(2-piperidinoethoxy)	3-morpholino	nn
41	4-(3-piperidinopropoxy)	3-morpholino	oo
42	4-[3-(4-methylpiperazin-1-yl)propoxy]	3-morpholino	pp
43	4-(2-diethylaminoethoxy)	3-morpholino	qq
44	4-(3-diethylaminopropoxy)	3-morpholino	rr
45	4-(2-diisopropylaminoethoxy)	3-morpholino	ss
46	4-(N-methylpiperidin-3-ylmethoxy)	3-morpholino	tt
47	4-(2-pyridylmethoxy)	3-morpholino	uu
48	4-(2-methylthiazol-4-ylmethoxy)	3-morpholino	vv
49	4-methoxy-3-(2-morpholinoethoxy)	3-morpholino	ww
50	4-methoxy-3-(3-morpholinopropoxy)	3-morpholino	xx
51	4-methoxy-3-(3-piperidinopropoxy)	3-morpholino	yy
52	4-methoxy-3-[3-(4-methylpiperazin-1-yl)propoxy]	3-morpholino	zz
53	4-methoxy-3-[2-(N-methylpyrrolidin-2-yl)ethoxy]	3-morpholino	aaa
54	4-methoxy-3-(N-methylpiperidin-3-ylmethoxy)	3-morpholino	bbb
55	3-(2-diethylaminoethoxy)-4-methoxy	3-morpholino	ccc
56	3-(3-diethylaminopropoxy)-4-methoxy	3-morpholino	ddd
57	3-(2-diisopropylaminoethoxy)-4-methoxy	3-morpholino	eee
58	4-methoxy-3-(2-methylthiazol-4-ylmethoxy)	3-morpholino	fff

Notes

a) The product had m.p. 114-116°C and gave the following data : NMR ($DMSOd_6$) 1.88 (m, 2H), 2.18 (s, 3H), 2.35 (t, 4H), 2.41 (t, 2H), 2.96 (s, 6H), 3.55 (t, 4H), 3.81 (s, 3H), 4.08 (t, 2H), 6.91 (m, 1H), 7.05 (d, 1H), 7.18 (m, 3H), 7.25 (t, 2H), 7.58 (m, 3H), 7.78 (d, 1H), 9.76 (s, 1H), 10.07 (br s, 1H); Mass M+H 547.

The N-[5-(3-dimethylaminobenzamido)-2-methylphenyl]-4-hydroxy-3-methoxybenzamide used as a starting material was prepared as follows :-

Oxalyl chloride (13.0 ml) was added dropwise to a stirred mixture of 3-dimethylaminobenzoic acid (20.3 g) and DMF (a few drops) which had been cooled to 0°C. The mixture was allowed to warm to ambient temperature and was stirred for 4 hours. The resultant mixture was evaporated and the residue was dissolved in methylene chloride (150 ml). 4-Methyl-3-nitroaniline (15.2 g) and triethylamine (27.9 ml) were added in turn and the resultant mixture was stirred at ambient temperature for 16 hours. The reaction mixture was washed in turn with water, with a saturated solution of sodium bicarbonate and with brine, dried ($MgSO_4$) and evaporated. The residue was triturated under a mixture of ethyl acetate and isohexane. The solid so obtained was filtered off and recrystallised from ethanol to give N-(3-nitro-4-methylphenyl)-3-dimethylaminobenzamide (6.1 g); NMR: ($DMSOd_6$) 2.46 (s, 3H), 2.95 (s, 6H), 6.92 (d, 1H), 7.22 (m, 2H), 7.32 (t, 1H), 7.45 (d, 1H), 7.97 (d, 1H), 8.53 (s, 1H), 10.43 (s, 1H); Mass M+H 300.

After repetition of the previous reactions, a sample (8.25 g) was added to a stirred suspension of ammonium formate (17.4 g), and 10% palladium-on-carbon (1 g) in methanol (250 ml). The mixture was stirred and heated to reflux for 4 hours. The mixture was allowed to cool and then filtered. The filtrate was evaporated and water was added to the residue. The resultant solid was isolated and washed in turn with water, with ethyl acetate and with diethyl ether. The solid was dried in a vacuum oven at 40°C to give N-(3-amino-4-methylphenyl)-3-dimethylaminobenzamide (6.89 g); NMR: ($DMSOd_6$) 2.0 (s, 3H), 2.94 (s, 6H), 4.78 (s, 2H), 6.82 (m, 3H), 7.07 (s, 1H), 7.17 (m, 2H), 7.25 (m, 1H), 9.74 (s, 1H); Mass M+H 270.

A solution of 3-methoxy-4-benzyloxybenzoyl chloride (3.01 g) in methylene chloride (50 ml) was added to a stirred suspension of N-(3-amino-4-methylphenyl)-

3-dimethylaminobenzamide (2.69 g) in methylene chloride (30 ml) and the reaction mixture was stirred at ambient temperature for 16 hours. The organic phase was washed with water and with a saturated aqueous sodium bicarbonate solution, dried and evaporated. The solid residue was stirred in diethyl ether for 16 hours, filtered and dried to give N-[5-(3-dimethylaminobenzamido)-2-methylphenyl]-3-methoxy-4-benzyloxybenzamide (0.458 g); NMR: ($DMSOd_6$) 2.18 (s, 3H), 2.96 (s, 6H), 3.82 (s, 3H), 5.12 (s, 2H), 6.9 (m, 1H), 7.16 (t, 1H), 7.21 (d, 2H), 7.3 (t, 2H), 7.4 (m, 5H), 7.57 (m, 3H), 7.78 (d, 1H), 9.75 (s, 1H), 10.18 (s, 1H).

After repetition of the preceding reaction, 10% palladium-on-carbon (0.25 g) was added to a stirred suspension of the material so obtained (2.55 g) in ethanol (100 ml) and the mixture was stirred at 25°C under 1 atmosphere pressure of hydrogen. After hydrogen uptake had ceased, the catalyst was removed by filtration and the filtrate was evaporated. The residue was crystallised under methanol to give the required phenolic starting material (1.90 g); NMR: ($DMSOd_6$) 2.18 (s, 3H), 2.97 (s, 6H), 3.82 (s, 3H), 6.82 (d, 1H), 6.9 (m, 1H), 7.17 (m, 3H), 7.27 (t, 1H), 7.5 (m, 1H), 7.77 (d, 1H), 9.58 (s, 1H), 9.62 (s, 1H), 10.06 (s, 1H).

b) The product gave the following data : NMR ($DMSOd_6$) 1.62 (m, 4H), 2.18 (s, 3H), 2.56 (t, 4H), 2.8 (t, 2H), 2.96 (s, 6H), 4.16 (t, 2H), 6.91 (m, 1H), 7.15 (m, 1H), 7.21 (m, 3H), 7.3 (t, 2H), 7.46 (t, 1H), 7.50 (s, 1H), 7.57 (m, 1H), 7.78 (d, 1H), 9.86 (s, 1H), 10.08 (s, 1H); Mass M+H 487.

The N-[5-(3-dimethylaminobenzamido)-2-methylphenyl]-3-hydroxybenzamide used as a starting material was prepared by reacting N-(3-amino-4-methylphenyl)-3-dimethylaminobenzamide with 3-benzyloxybenzoyl chloride using an analogous procedure to that described in Note a) above to give an intermediate benzyloxy compound which was hydrogenated over 10% palladium-on-carbon as also described in Note a) above to give the required phenolic starting material, m.p. 224-227°C; NMR: ($DMSOd_6$) 2.18 (s, 3H), 2.97 (s, 6H), 6.9 (m, 1H), 6.97 (m, 1H), 7.2 (m, 3H), 7.3 (m, 3H), 7.38 (d, 1H), 7.48 (m, 1H), 7.78 (d, 1H), 9.7 (br s, 1H), 9.79 (s, 1H), 10.07 (br s, 1H).

c) The product gave the following data : NMR ($DMSOd_6$) 2.18 (s, 3H), 2.46 (t, 4H), 2.71 (t, 2H), 2.96 (s, 6H), 3.57 (t, 4H), 4.18 (t, 2H), 6.9 (m, 1H), 7.18 (m, 1H), 7.21 (m, 3H),

7.28 (t, 1H), 7.42 (t, 1H), 7.58 (m, 3H), 7.79 (d, 1H), 9.82 (s, 1H), 10.08 (s, 1H); Mass M+H 503.

d) The product gave the following data : NMR ($DMSOd_6$) 2.18(s, 3H), 2.42 (t, 4H), 2.7 (t, 2H), 2.96 (s, 6H), 3.58 (t, 4H), 4.18 (t, 2H), 6.9 (m, 1H), 7.03 (d, 2H), 7.20 (m, 3H), 7.27 (t, 1H), 7.57 (m, 1H), 7.78 (d, 1H), 7.96 (d, 2H), 9.71 (s, 1H), 10.08 (s, 1H); Mass M+H 503.

e) The product gave the following data : NMR ($DMSOd_6$) 1.89 (m, 2H), 2.18 (s, 3H), 2.36 (t, 4H), 2.41 (t, 2H), 2.96 (s, 6H); 3.57 (t, 4H), 4.07 (t, 2H), 6.9 (m, 1H), 7.16 (m, 1H), 7.2 (m, 3H), 7.26 (t, 2H), 7.4 (t, 1H), 7.54 (m, 3H), 7.79 (d, 1H), 9.82 (s, 1H), 10.08 (s, 1H); Mass M+H 517.

f) The product gave the following data : NMR ($DMSOd_6$) 2.18 (s, 3H), 2.42 (m, 6H), 2.7 (t, 2H), 2.96 (s, 6H), 3.58 (t, 4H), 3.81 (s, 3H), 4.08 (t, 2H), 6.88 (m, 1H), 7.08 (d, 1H), 7.2 (m, 3H), 7.27 (t, 1H), 7.58 (m, 3H), 7.78 (d, 1H), 9.77 (s, 1H), 10.07 (br s, 1H); Mass M+H 533.

g) The product gave the following data : NMR ($DMSOd_6$) 1.37 (m, 2H), 1.42 (m, 4H), 2.18 (s, 1H), 2.42 (t, 4H), 2.62 (t, 2H), 2.96 (s, 6H), 3.82 (s, 3H), 4.16 (t, 2H), 6.91 (m, 1H), 7.05 (d, 1H), 7.18 (m, 3H), 7.26 (t, 1H), 7.58 (m, 3H), 7.78 (d, 1H), 9.72 (s, 1H), 10.07 (s, 1H); Mass M+H 531.

The N-[5-(3-dimethylaminobenzamido)-2-methylphenyl]-3-hydroxy-4-methoxybenzamide used as a starting material was prepared by reacting N-(3-amino-4-methylphenyl)-3-dimethylaminobenzamide with 3-benzyloxy-4-methoxybenzoyl chloride using an analogous procedure to that described in Note a) above to give the intermediate benzyloxy compound which was hydrogenated over 10% palladium-on-carbon as also described in Note a) above to give the required phenolic starting material, m.p. 136-138°C; NMR: ($DMSOd_6$) 2.18 (s, 3H), 2.97 (s, 6H), 3.82 (s, 3H), 6.9 (m, 1H), 7.0 (m, 1H), 7.18 (m, 3H), 7.25 (t, 1H), 7.40 (d, 1H), 7.48 (m, 1H) 7.57 (m, 1H), 7.78 (d, 1H), 9.2 (s, 1H), 9.62 (s, 1H), 10.06 (s, 1H).

h) The product gave the following data : NMR ($DMSOd_6$) 1.64 (t, 4H), 2.18 (s, 3H), 2.52 (t, 4H), 2.8 (t, 2H), 2.96 (s, 6H), 3.81 (s, 3H), 4.12 (t, 2H), 6.9 (m, 1H), 7.07 (d, 1H), 7.19 (m, 3H), 7.26 (t, 1H), 7.58 (m, 3H), 7.78 (d, 1H), 9.73 (s, 1H), 10.07 (s, 1H); Mass M+H 517.

i) The product gave the following data : NMR ($DMSOd_6$) 1.9 (m, 2H), 2.18 (s, 3H), 2.37 (t, 4H), 2.42 (t, 2H), 2.96 (s, 6H), 3.57 (t, 4H), 3.81 (s, 3H), 4.07 (t, 2H), 6.9 (m, 1H), 7.05 (d, 1H), 7.20 (m, 3H), 7.28 (t, 1H), 7.56 (m, 2H), 7.61 (m, 1H), 7.78 (d, 1H), 9.75 (s, 1H), 10.57 (s, 1H); Mass M+H 547.

j) The product gave the following data : NMR ($DMSOd_6$) 2.18 (t, 3H), 2.43 (t, 4H), 2.7 (t, 2H), 2.97 (s, 6H), 3.57 (t, 4H), 3.82 (s, 3H), 4.17 (t, 2H), 6.9 (m, 1H), 7.06 (d, 1H), 7.19 (m, 3H), 7.26 (t, 1H), 7.61 (m, 3H), 7.78 (d, 1H), 9.78 (s, 1H), 10.07 (s, 1H); Mass M+H 533.

k) The product gave the following data : NMR ($DMSOd_6$) 2.18 (s, 3H), 2.97 (s, 6H), 5.26 (s, 2H), 6.9 (m, 1H), 7.18 (d, 2H), 7.2 (m, 3H), 7.29 (t, 2H), 7.35 (m, 1H), 7.57 (m, 2H), 7.82 (m, 2H), 7.95 (d, 2H), 8.58 (d, 1H), 9.72 (s, 1H), 10.07 (s, 1H); Mass M+H 481.

l) The product gave the following data : NMR ($DMSOd_6$) 2.18 (s, 3H), 2.96 (s, 6H), 5.25 (s, 2H), 6.9 (m, 1H), 7.29 (m, 6H), 7.42 (t, 1H), 7.56 (m, 4H), 7.81 (m, 2H), 8.58 (d, 1H), 9.82 (s, 1H), 10.08 (s, 1H); Mass M+H 481.

m) The alkylating agent was 2-bromoethyl methyl ether. The product gave the following data : NMR ($DMSOd_6$) 2.18 (s, 3H), 2.95 (s, 6H), 3.67 (m, 2H), 4.17 (m, 2H), 6.85 (d, 1H), 7.04 (d, 2H), 7.24 (m, 4H), 7.58 (d, 1H), 7.78 (s, 1H), 7.96 (d, 2H), 9.42 (s, 1H), 10.09 (s, 1H); Mass M+H 448.

n) The product gave the following data : NMR ($DMSOd_6$) 1.38 (s, 4H), 2.21 (s, 3H), 2.38 (t, 4H), 2.81 (t, 4H), 2.97 (s, 6H), 4.35 (t, 4H), 6.89 (m, 1H), 7.11 (t, 1H), 7.25 (m, 6H), 7.55 (m, 2H), 7.94 (d, 1H), 7.95 (s, 1H), 10.07 (br s, 1H), 10.26 (br s, 1H); Mass M+H 487.

The N-[5-(3-dimethylaminobenzamido)-2-methylphenyl]-2-hydroxybenzamide used as a starting material was prepared as follows :-

A solution of 2-benzyloxybenzoyl chloride (2.69 g) in methylene chloride (50 ml) was added dropwise to a stirred mixture of N-(3-amino-4-methylphenyl)-3-dimethylaminobenzamide (2.69 g), pyridine (3 ml) and methylene chloride (50 ml) which had been cooled to 5°C. The reaction mixture was stirred for 16 hours at ambient temperature. The organic phase was washed with water and with a saturated aqueous sodium bicarbonate solution, dried ($MgSO_4$) and evaporated. The residue was stirred under diethyl ether for 16 hours to give a precipitate which was isolated and dried.

There was this obtained N-[5-(3-dimethylaminobenzamido)-2-methylphenyl]-2-benzyloxybenzamide (4.3 g), m.p. 136-139°C; NMR: ($DMSOd_6$) 1.85 (s, 3H), 2.98 (s, 6H), 5.36 (s, 2H), 6.9 (d, 1H), 7.12 (m, 2H), 7.33 (m, 7H), 7.52 (m, 4H), 7.9 (d, 1H), 8.12 (s, 1H), 9.7 (s, 1H), 10.08 (br s, 1H); Mass: M+H 480.

10% Palladium-on-carbon (0.25 g) was added to a stirred suspension of a portion (2.4 g) of the material so obtained in ethanol (125 ml) and the resultant mixture was stirred at ambient temperature under 1 atmosphere pressure of hydrogen. After uptake of hydrogen had ceased, the catalyst was removed by filtration and the filtrate was evaporated. The residue was triturated under methanol. There was thus obtained the required starting material (1.36 g), m.p. 234-238°C; NMR: ($DMSOd_6$) 2.22 (s, 3H), 2.97 (s, 6H), 6.92 (m, 3H), 7.21 (m, 3H), 7.3 (q, 1H), 7.42 (m, 1H), 7.57 (m, 1H), 8.02 (m, 1H), 8.21 (d, 1H), 10.15 (br s, 1H), 10.38 (br s, 1H); Mass: M+H 390.

o) The product gave the following data : NMR ($DMSOd_6$) 1.63 (m, 4H), 2.18 (s, 3H), 2.52 (t, 4H), 2.78 (t, 2H), 2.96 (s, 6H), 4.18 (t, 2H), 6.9 (m, 1H), 7.03 (d, 2H), 7.18 (m, 3H), 7.25 (t, 1H), 7.56 (m, 1H), 7.78 (d, 1H), 7.94 (d, 2H), 9.73 (s, 1H), 10.07 (s, 1H); Mass M+H 487.

p) The product gave the following data : NMR ($DMSOd_6$) 1.62 (s, 4H), 2.16 (s, 3H), 2.46 (s, 4H), 2.8 (t, 2H), 2.96 (s, 6H), 3.82 (s, 3H), 4.1 (t, 2H), 6.88 (m, 1H), 7.08 (d, 1H), 7.2 (d, 3H), 7.27 (t, 1H), 7.48 (m, 4H), 7.78 (s, 1H), 9.75 (s, 1H), 10.07 (s, 1H); Mass M+H 517.

q) The product gave the following data : NMR ($DMSOd_6$) 2.18 (s, 3H), 2.94 (s, 6H), 3.83 (s, 3H), 5.23 (s, 2H), 6.9 (m, 1H), 7.14 (d, 1H), 7.2 (m, 3H), 7.26 (t, 1H), 7.35 (m, 1H), 7.53 (m, 4H), 7.77 (d, 1H), 7.82 (m, 1H), 8.58 (d, 1H), 9.75 (s, 1H), 10.07 (br s, 1H); Mass M+H 511.

r) The product gave the following data : NMR ($DMSOd_6$) 1.41 (s, 9H), 2.18 (s, 3H), 2.94 (s, 6H), 3.82 (s, 3H), 5.23 (s, 2H), 6.9 (m, 1H), 6.94 (d, 1H), 7.2 (m, 3H), 7.26 (t, 1H), 7.57 (m, 3H), 7.77 (d, 1H), 9.78 (s, 1H), 10.08 (s, 1H); Mass M+H 532.

s) The product gave the following data : NMR ($DMSOd_6$) 1.62 (t, 4H), 2.19 (s, 3H), 2.52 (t, 4H), 2.8 (t, 2H), 3.17 (t, 4H), 3.76 (t, 4H), 4.16 (t, 2H), 6.9 (m, 1H), 7.15 (m, 1H), 7.21 (m, 3H), 7.3 (t, 2H), 7.4 (t, 1H), 7.51 (s, 1H), 7.57 (m, 1H), 7.78 (s, 1H), 9.7 (s, 1H), 9.9 (s, 1H); Mass M+H 529.

The N-[2-methyl-5-(3-morpholinobenzamido)phenyl]-3-hydroxybenzamide used as a starting material was prepared as follows :-

A solution of 3-morpholinobenzoyl chloride (0.24 g) in methylene chloride (5 ml) was added to a stirred mixture of 4-methyl-3-nitroaniline (0.15 g), pyridine (0.24 ml) and methylene chloride (10 ml). The reaction mixture was stirred at ambient temperature for 16 hours. The organic phase was washed with water and with a saturated aqueous sodium bicarbonate solution. The organic layer was dried ($MgSO_4$) and evaporated. The residual solid was triturated under diethyl ether and the resultant solid was isolated and dried to give N-(3-nitro-4-methylphenyl)-3-morpholinobenzamide (0.28 g); NMR : ($DMSOd_6$) 3.2 (t, 4H), 3.3 (s, 3H), 3.78 (t, 4H), 7.19 (s, 1H), 7.4 (m, 2H), 7.47 (d, 2H), 8.0 (d, 1H), 8.83 (s, 1H), 10.23 (s, 1H).

10% Palladium-on-carbon (0.035 g) was added to a stirred solution in methanol (40 ml) of the nitro compound so obtained (0.28 g) and the mixture was stirred at ambient temperature under 1 atmosphere pressure of hydrogen. After uptake of hydrogen had ceased, the catalyst was removed by filtration and the filtrate was evaporated to give N-(3-amino-4-methylphenyl)-3-morpholinobenzamide; NMR: ($DMSOd_6$) 2.0 (s, 3H), 3.19 (t, 4H), 3.78 (t, 4H), 4.8 (s, 2H), 6.8 (q, 2H), 7.08 (s, 1H), 7.1 (d, 1H), 7.34 (m, 2H), 7.4 (s, 1H), 9.8 (s, 1H); Mass: M+H 312.

After repetition of the preceding steps, a solution of 3-benzyloxybenzoyl chloride (1.33 g) in methylene chloride (20 ml) was added to a stirred mixture of N-(3-amino-4-methylphenyl)-3-morpholinobenzamide (1.55 g), pyridine (1 ml) and methylene chloride (20 ml). The reaction mixture was stirred at ambient temperature for 18 hours. The organic phase was washed with water and with a saturated aqueous sodium bicarbonate solution, dried ($MgSO_4$) and evaporated. The residue was stirred under diethyl ether for 20 hours. The precipitate was isolated and dried. There was thus obtained N-[2-methyl-5-(3-morpholinobenzamido)phenyl]-3-benzyloxybenzamide (2.21 g); m.p. 192-193°C; NMR: ($DMSOd_6$) 2.18 (s, 3H), 3.16 (t, 4H), 3.76 (t, 4H), 5.18 (s, 2H), 7.15 (d, 1H), 7.21 (d, 2H), 7.4 (m, 9H), 7.56 (d, 2H), 7.58 (s, 1H), 7.8 (d, 1H), 9.85 (s, 1H), 10.12 (br s, 1H); Mass: M+H 522.

10% Palladium-on-carbon catalyst (0.2 g) was added to a stirred suspension of a portion (1.94 g) of the material so obtained in ethanol (200 ml) The mixture was stirred

at ambient temperature under 1 atmosphere pressure of hydrogen. After cessation of hydrogen uptake, the catalyst was removed and the filtrate was evaporated. The residue was triturated under methanol. There was thus obtained the required starting material (0.825 g), m.p. 227-229°C; NMR: ($DMSOd_6$) 2.19 (s, 3H), 3.18 (t, 4H), 3.77 (t, 4H), 6.98 (m, 1H), 7.15 (m, 1H), 7.21 (d, 1H), 7.31 (t, 1H), 7.38 (m, 5H), 7.58 (m, 1H), 7.78 (s, 1H), 9.68 (s, 1H), 9.78 (s, 1H), 10.1 (s, 1H); Mass: M+H 432.

The 3-morpholinobenzoyl chloride used as a starting material was prepared as follows:-

A mixture of ethyl 3-bromobenzoate (1.92 ml), morpholine (1.25 ml), 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (0.336 g), sodium tert-butoxide (1.615 g) and tris(dibenzylideneacetone)dipalladium(0) (0.33 g) and toluene (25 ml) was stirred and heated to 90°C for 18 hours under argon. The reaction mixture was allowed to cool to ambient temperature and extracted with 1N aqueous hydrochloric acid. The aqueous phase was basified with concentrated sodium hydroxide solution and extracted with ethyl acetate. The organic phase was dried ($MgSO_4$) and evaporated. The residual oil was purified by column chromatography on silica gel using a 47:3 mixture of methylene chloride and methanol as eluent. There was thus obtained N-(3-morpholinobenzoyl)morpholine (0.45 g).

A mixture of the material so obtained, 5M sodium hydroxide solution (2.5 ml) and butanol (2 ml) was stirred and heated to 115°C for 18 hours. The mixture was evaporated and the residue was acidified by the addition of 1N aqueous hydrochloric acid solution (12.5 ml). The resultant precipitate was isolated, washed with water and dried to give 3-morpholinobenzoic acid (0.15 g); NMR ($DMSOd_6$) 3.1 (t, 4H), 3.73 (t, 4H), 7.19 (d, 1H), 7.32 (d, 1H), 7.38 (t, 1H), 7.42 (s, 1H).

Oxalyl chloride (0.14 ml) was added to a solution of 3-morpholinobenzoic acid (0.28 g) in methylene chloride (10 ml) which contained DMF (2 drops). The reaction mixture was stirred for 18 hours at ambient temperature. The mixture was evaporated and azeotroped with toluene to give 3-morpholinobenzoyl chloride (0.3 g); Mass M+H 222.

t) The product gave the following data : NMR ($DMSOd_6$) 1.31 (m, 2H), 1.45 (m, 4H), 2.19 (s, 3H), 2.45 (t, 4H), 2.71 (t, 2H), 3.19 (t, 4H), 3.76 (t, 4H), 4.18 (t, 2H), 7.13 (d, 2H),

7.22 (d,1H), 7.4 (m, 3H), 7.43 (s, 1H), 7.53 (s, 2H), 7.57 (d, 1H), 7.78 (d, 1H), 9.82 (s, 1H), 10.1 (s, 1H); Mass M+H 543.

u) The product gave the following data : NMR ($DMSOd_6$) 2.18 (s, 3H), 2.46 (t, 4H), 2.7 (t, 2H), 3.18 (t, 4H), 3.57 (t, 4H), 3.76 (t, 4H), 4.17 (t, 2H), 7.17 (m, 2H), 7.21 (d, 1H), 7.37 (m, 2H), 7.42 (m, 2H), 7.57 (m, 3H), 7.78 (d, 1H), 9.85 (s, 1H), 10.1 (s, 1H); Mass M+H 545.

v) The product gave the following data : NMR ($DMSOd_6$) 0.98 (t, 6H), 1.98 (s, 3H), 2.56 (q, 4H), 2.78 (t, 2H), 3.18 (t, 4H), 3.77 (t, 4H), 4.08 (t, 2H), 7.14 (d, 2H), 7.21 (d, 1H), 7.36 (m, 2H), 7.41 (m, 2H), 7.5 (m, 2H), 7.57 (m, 1H), 7.78 (d, 1H), 9 .82 (s, 1H), 10.11 (s, 1H); Mass M+H 531.

w) The product gave the following data : NMR ($DMSOd_6$) 2.22 (s, 3H), 3.22 (t, 4H), 3.79 (t, 4H), 5.23 (s, 2H), 7.12 (m, 1H), 7.28 (t, 3H), 7.42 (m, 3H), 7.48 (t, 2H), 7.6 (d, 1H), 7.62 (s, 1H), 7.65 (d, 1H), 7.85 (s, 1H), 7.9 (m, 1H), 8.6 (d, 1H), 9.9 (s, 1H), 10.15 (s, 1H); Mass M+H 523.

x) The product gave the following data : NMR ($DMSOd_6$) 1.62 (t, 4H), 2.18 (s, 3H), 2.47 (t, 4H), 2.8 (t, 2H), 3.18 (t, 4H), 3.76 (t, 4H), 3.84 (s, 3H), 4.13 (t, 2H), 7.04 (d, 1H), 7.07 (m, 1H), 7.19 (d, 1H), 7.37 (m, 3H), 7.41 (s, 1H), 7.57 (m, 2H), 7.78 (s, 1H), 9.73 (s, 1H), 10.11 (s, 1H); Mass M+H 559.

The N-[2-methyl-5-(3-morpholinobenzamido)phenyl]-3-hydroxy-4-methoxybenzamide used as a starting material was prepared by reacting N-(3-amino-4-methylphenyl)-3-morpholinobenzamide with 3-benzyloxy-4-methoxybenzoyl chloride using an analogous procedure to that described in Note a) above to give an intermediate benzyloxy compound which was hydrogenated over 10% palladium-on-carbon as also described in Note a) above to give the required phenolic starting material; NMR ($DMSOd_6$) 2.16 (s, 3H), 3.18 (t, 4H), 3.78 (t, 4H), 3,82 (s, 3H), 7.01 (m, 1H), 7.14 (t, 1H), 7.18 (d, 1H), 7.35 (m, 6H), 7.58 (m, 1H), 9.21 (s, 1H), 9.53 (s, 1H), 10.1 (br s, 1H); Mass M+H 462.

y) The product gave the following data : NMR ($DMSOd_6$) 1.32 (m, 2H), 1.44 (m, 4H), 2.18 (s, 3H), 2.39 (t, 4H),2.62 (t, 2H), 3.18 (t, 4H), 3.78 (t, 4H), 3.81 (s, 3H), 4.12 (t, 2H), 7.07 (d, 1H), 7.16 (m, 1H), 7.21 (d, 1H), 7.37 (m, 2H), 7.42 (s, 1H), 7.57 (m, 3H), 7.78 (s, 1H), 9.73 (s, 1H), 10.11 (s, 1H); Mass M+H 573.

z) The product gave the following data : NMR ($DMSOd_6$) 2.18 (s, 3H), 3.18 (t, 4H), 3.77 (t, 4H), 3.83 (s, 3H), 5.21 (s, 2H), 7.1 (d, 2H), 7.21 (d, 1H), 7.37 (m, 3H), 7.42 (s, 1H), 7.57 (m, 2H), 7.64 (m, 2H), 7.77 (s, 1H), 7.82 (m, 1H), 8.58 (d, 1H), 9.73 (s, 1H), 10.1 (s, 1H); Mass M+H 553.

aa) The product gave the following data : Mass M+H 515.

bb) The product gave the following data : NMR ($DMSOd_6$) 1.36 (d, 2H), 1.46 (m, 4H), 1.86 (m, 2H), 2.18 (s, 3H), 2.4 (m, 6H), 3.19 (t, 4H), 3.75 (t, 4H), 4.06 (t, 2H), 7.11 (d, 2H), 7.22 (d, 1H), 7.39 (m, 3H), 7.56 (m, 3H), 7.78 (s, 1H), 9.86 (s, 1H), 10.11 (s, 1H); Mass M+H 557.

cc) The reactants were heated to 100°C for 24 hours. The product gave the following data : NMR ($DMSOd_6$) 1.9 (m, 2H), 2.19 (s, 3H), 2.38 (t, 4H), 2.4 (d, 2H), 3.18 (t, 4H), 3.57 (t, 4H), 3.78 (t, 4H), 4.08 (t, 2H), 7.12 (d, 2H), 7.21 (d, 1H), 7.37 (m, 4H), 7.57 (m, 3H), 7.78 (d, 1H), 9.82 (s, 1H), 10.11 (s, 1H); Mass M+H 559.

dd) The product gave the following data : NMR ($DMSOd_6$) 0.97 (d, 12H), 2.19 (s, 3H), 2.78 (t, 2H), 3.01 (t, 3H), 3.18 (t, 4H), 3.74 (t, 4H), 3.93 (t, 4H), 7.1 (m, 2H), 7.21 (d, 1H), 7.4 (m, 4H), 7.52 (m, 3H), 7.79 (s, 1H), 9.85 (s, 1H), 10.11 (s, 1H); Mass M+H 559.

ee) The product gave the following data : NMR ($DMSOd_6$) 0.96 (t, 6H), 1.83 (m, 2H), 2.19 (s, 3H), 2.48 (m, 6H), 3.17 (t, 4H), 3.72 (t, 4H), 4.07 (t, 2H), 7.1 (m, 2H), 7.12 (d, 1H), 7.39 (m, 4H), 7.53 (m, 3H), 7.78 (s, 1H), 9.83 (s, 1H), 10.11 (s, 1H); Mass M+H 545.

ff) The reaction product was purified by column chromatography on silica using a 9:1 mixture of methylene chloride and methanol as eluent. The product so obtained gave the following data : NMR ($DMSOd_6$) 1.7 (m, 5H), 2.04 (m, 2H), 2.17 (s, 3H), 2.23 (d, 3H), 3.18 (t, 4H), 3.75 (t, 4H), 4.07 (t, 1H), 7.1 (m, 2H), 7.22 (d, 1H), 7.4 (m, 4H), 7.53 (m, 3H), 7.78 (s, 1H), 9.85 (d, 1H), 10.11 (s, 1H); Mass M+H 543.

gg) The reactants were stirred at 25°C for 36 hours rather than being heated to 60°C. The product gave the following data : NMR ($DMSOd_6$) 2.19 (s, 3H), 3.18 (t, 4H), 3.78 (t, 4H), 5.21 (s, 2H), 7.12 (d, 2H), 7.37 (m, 5H), 7.57 (m, 2H), 7.6 (s, 1H), 7.78 (d, 1H) 7.86 (d, 1H), 8.54 (d, 1H), 8.7 (s, 1H), 9.95 (s, 1H), 10.11 (s,1H); Mass M+H 523.

hh) The reactants were stirred at 25°C for 36 hours rather than being heated to 60°C. The product gave the following data : NMR ($DMSOd_6$) 2.14 (s, 3H), 3.15 (t, 4H), 3.74 (t,

4H), 5.28 (s, 2H), 7.1 (m, 1H), 7.21 (m, 2H), 7.37 (m, 2H), 7.45 (m, 4H), 7.57 (m, 3H), 7.78 (s, 1H), 8.58 (d, 2H), 9.91 (s, 1H), 10.12 (s, 1H); Mass M+H 523.

ii) The product gave the following data : NMR ($DMSOd_6$) 2.2 (s, 3H), 2.63 (s, 3H), 3.18 (t, 4H), 3.76 (t, 4H), 5.18 (s, 1H), 7.11 (d, 1H), 7.23 (t, 2H), 7.36 (m, 2H), 7.42 (t, 2H), 7.59 (m, 4H), 7.79 (s, 1H), 9.84 (s, 1H), 10.11 (s, 1H); Mass M+H 543.

jj) The product gave the following data : NMR ($DMSOd_6$) 1.05 (t, 4H), 2.18 (d, 6H), 3.19 (s, 4H), 3.73 (s, 4H), 3.89 (t, 2H), 7.1 (d, 2H), 7.19 (d, 1H), 7.39 (m, 4H), 7.53 (m, 3H), 7.79 (s, 1H), 9.85 (s, 1H), 10.1 (s, 1H); Mass M+H 543.

kk) The product gave the following data : NMR ($DMSOd_6$) 2.19 (s, 3H), 2.7 (t, 2H), 3.17 (t, 3H), 3.28 (m, 4H), 3.57 (t, 4H), 3.76 (t, 4H), 4.17 (t, 2H), 7.04 (d, 2H), 7.11 (m, 1H), 7.19 (d, 1H), 7.35 (m, 2H), 7.42 (s, 1H), 7.55 (m, 1H), 7.77 (s, 1H), 7.92 (m, 2H), 9.7 (s, 1H), 10.1 (s, 1H); Mass M+H 545.

The N-[2-methyl-5-(3-morpholinobenzamido)phenyl]-4-hydroxybenzamide used as a starting material was prepared as follows :-

A solution of 4-benzyloxybenzoyl chloride [obtained by the reaction of 4-benzyloxybenzoic acid (8.66 g) and oxalyl chloride (4 ml)] in methylene chloride (300 ml) was added to a stirred mixture of N-(3-amino-4-methylphenyl)-3-morpholinobenzamide (10.6 g), pyridine (5.42 ml) and methylene chloride (300 ml). The reaction mixture was stirred at ambient temperature for 18 hours. The organic phase was washed with water and with a saturated aqueous sodium bicarbonate solution, dried ($MgSO_4$) and evaporated. The residue was stirred under diethyl ether for 2 hours. The precipitate was isolated and dried. There was thus obtained N-[2-methyl-5-(3-morpholinobenzamido)phenyl]-4-benzyloxybenzamide (16.1 g); NMR: ($DMSOd_6$) 2.19 (s, 3H), 3.17 (t, 4H), 3.75 (t, 4H), 5.19 (s, 2H), 7.11 (d, 2H), 7.2 (d, 1H), 7.39 (m, 9H), 7.58 (m, 1H), 7.79 (s, 1H), 7.97 (d, 2H), 9.71 (s, 1H), 10.1 (s, 1H); Mass: M+H 522.

10% Palladium-on-carbon catalyst (1.8 g) was added to a stirred suspension of a portion (14.6 g) of the material so obtained in methanol (750 ml) The mixture was stirred at ambient temperature under 1 atmosphere pressure of hydrogen. After cessation of hydrogen uptake, the catalyst was removed and the filter cake was washed with warm DMF (500 ml). The filtrate was concentrated to a volume of approximately 50 ml and poured into water. The solid so obtained was isolated and dried. There was thus

obtained the required starting material (9.95 g), NMR: ($DMSOd_6$) 2.19 (s, 3H), 3.18 (t, 4H), 3.74 (t, 4H), 6.93 (m, 1H), 7.15 (m, 1H), 7.21 (d, 1H), 7.37 (m, 6H), 7.58 (m, 1H), 7.78 (s, 1H), 9.83 (s, 1H), 10.1 (s, 1H); Mass: M-H 430.

ll) The product gave the following data : NMR ($DMSOd_6$) 1.87 (m, 2H), 2.18 (s, 3H), 2.42 (m, 2H), 3.17 (t, 4H), 3.54 (t, 4H), 3.75 (t, 4H), 4.07 (t, 2H), 7.03 (d, 2H), 7.12 (m, 1H), 7.2 (d, 1H), 7.34 (m, 2H), 7.42 (s, 1H), 7.57 (m, 1H), 7.78 (s, 1H), 7.93 (d, 2H), 9.69 (s, 1H), 10.1 (s, 1H); Mass M+H 559.

mm) The product gave the following data : NMR ($DMSOd_6$) 1.67 (s, 4H), 2.18 (s, 3H), 2.81 (t, 2H), 3.18 (t, 4H), 3.74 (t, 4H), 4.17 (t, 2H), 7.04 (d, 2H), 7.14 (m, 1H), 7.21 (d, 1H), 7.37 (m, 2H), 7.43 (s, 1H), 7.57 (m, 1H), 7.79 (s, 1H), 7.96 (d, 2H), 9.7 (s, 1H), 10.1 (s, 1H); Mass M+H 529.

nn) The product gave the following data : NMR ($DMSOd_6$) 1.36 (m, 2H), 1.47 (m, 4H), 2.17 (s, 3H), 2.41 (m, 4H), 2.65 (t, 2H), 3.17 (t, 4H), 3.74 (t, 4H), 4.16 (t, 2H), 7.03 (d, 2H), 7.12 (m, 1H), 7.19 (d, 1H), 7.36 (m, 2H), 7.43 (s, 1H), 7.56 (m, 1H), 7.78 (m, 1H), 7.95 (d, 2H), 9.7 (s, 1H), 10.1 (s, 1H); Mass M+H 543.

oo) The product gave the following data : NMR ($DMSOd_6$) 1.34 (m, 2H), 1.49 (m, 4H), 1.86 (m, 2H), 2.19 (s, 3H), 2.37 (m, 6H), 3.19 (t, 4H), 3.76 (t, 4H), 4.07 (t, 2H), 7.02 (d, 2H), 7.12 (m, 1H), 7.2 (d, 1H), 7.37 (m, 2H), 7.43 (s, 1H), 7.58 (d, 1H), 7.79 (s, 1H), 7.95 (d, 2H), 9.72 (s, 1H), 10.09 (s, 1H); Mass M+H 557.

pp) The product gave the following data : NMR ($DMSOd_6$) 1.85 (m, 2H), 2.16 (d, 6H), 2.37 (m, 10H), 3.17 (t, 4H), 3.75 (t, 4H), 4.05 (t, 2H), 7.02 (d, 2H), 7.12 (m, 1H), 7.2 (d, 1H), 7.36 (m, 2H), 7.43 (s, 1H), 7.56 (m, 1H), 7.78 (s, 1H), 7.95 (d, 2H), 9.7 (s, 1H), 10.1 (s, 1H); Mass M+H 572.

qq) The product gave the following data : NMR ($DMSOd_6$) 0.96 (t, 6H), 2.18 (s, 3H), 2.56 (m, 4H), 2.68 (t, 2H), 3.18 (t, 4H), 3.75 (t, 4H), 4.08 (t, 2H), 7.02 (d, 2H), 7.1 (m, 1H), 7.20 (d, 1H), 7.35 (m, 2H), 7.43 (s, 1H), 7.54 (m, 1H), 7.78 (s, 1H), 7.93 (d, 2H), 9.68 (s, 1H), 10.1 (s, 1H); Mass M+H 531.

rr) The product gave the following data : NMR ($DMSOd_6$) 0.95 (t, 6H), 1.82 (m, 2H), 2.18 (s, 3H), 2.46 (m, 6H), 3.18 (t, 4H), 3.74 (t, 4H), 4.06 (t, 2H), 7.01 (d, 2H), 7.12 (m, 1H), 7.19 (d, 1H), 7.35 (m, 2H), 7.42 (s, 1H), 7.56 (m, 1H), 7.77 (d, 1H), 7.94 (d, 2H), 9.7 (s, 1H), 10.09 (s, 1H); Mass M+H 545.

ss) The product gave the following data : NMR ($DMSOd_6$) 0.97 (d, 12H), 2.19 (s, 3H), 2.78 (t, 2H), 3.01 (m, 2H), 3.18 (t, 4H), 3.74 (t, 4H), 3.95 (t, 2H), 7.01 (d, 2H), 7.13 (m, 1H), 7.2 (d, 1H), 7.37 (m, 2H), 7.43 (s, 1H), 7.55 (m, 1H), 7.77 (d, 1H), 7.95 (d, 2H), 9.7 (s, 1H), 10.09 (s, 1H); Mass M+H 559.

tt) The product gave the following data : NMR ($DMSOd_6$) 1.05 (m, 1H), 1.7 (m, 6H), 2.17 (d ,6H), 2.61 (m, 1H), 2.79 (m, 1H), 3.17 (t, 4H), 3.74 (t, 4H), 3.91 (m, 2H), 7.03 (d, 2H), 7.12 (m, 1H), 7.2 (d, 1H), 7.35 (m, 2H), 7.42 (s, 1H), 7.55 (m, 1H), 7.77 (s, 1H), 7.95 (d, 2H), 9.69 (s, 1H), 10.09 (s, 1H); Mass M+H 543.

uu) The product gave the following data : NMR ($DMSOd_6$) 2.19 (s, 3H), 3.18 (t, 4H), 3.73 (t, 4H), 5.23 (s, 2H), 7.12 (d, 3H), 7.2 (d, 1H), 7.34 (m, 3H), 7.42 (s, 1H), 7.54 (m, 2H), 7.8 (m, 2H), 7.97 (d, 2H), 8.58 (d, 1H), 9.72 (s, 1H), 10.1 (s, 1H); Mass M+H 523.

vv) The product gave the following data : NMR ($DMSOd_6$) 2.19 (s, 3H), 2.63 (s, 3H), 3.17 (t, 4H), 3.75 (t, 4H), 5.19 (s, 2H), 7.1 (d, 3H), 7.2 (d, 1H), 7.37 (m, 2H), 7.43 (s, 1H), 7.57 (m, 2H), 7.79 (d, 1H), 7.95 (d, 2H), 9.72 (s, 1H), 10.1 (s,1H); Mass M+H 543.

ww) The reactants were heated to 100°C for 24 hours. The product gave the following data : NMR ($DMSOd_6$) 2.18 (s, 3H), 2.42 (t, 4H), 2.7 (t, 2H), 3.18 (t, 4H), 3.56 (t, 4H), 3.77 (t, 4H), 3.82 (s, 3H), 4.17 (t, 2H), 7.05 (d, 1H), 7.15 (m, 1H), 7.21 (d, 1H), 7.35 (m, 2H), 7.42 (s, 1H), 7.58 (m, 3H), 7.78 (s, 1H), 9.75 (s, 11H), 10.1 (s, 1H); Mass M+H 575.

xx) The reactants were heated to 100°C for 24 hours. The product gave the following data : NMR ($DMSOd_6$) 1.82 (m, 2H), 2.15 (s, 3H), 2.37 (t, 4H), 2.4 (t, 2H), 3.18 (t, 4H), 3.56 (t, 4H), 3.76 (t, 4H), 4.03 (t, 2H), 7.02 (d, 1H), 7.12 (m, 1H), 7.2 (d, 1H), 7.37 (m, 2H), 7.41 (s, 1H), 7.52 (m, 2H), 7.6 (m, 1H), 7.78 (d, 1H), 9.75 (s, 1H), 10.1 (s, 1H); Mass M+H 589.

yy) The reactants were heated to 100°C for 24 hours. The product gave the following data : NMR ($DMSOd_6$) 1.42 (m, 2H), 1.56 (m, 4H), 1.96 (m, 2H), 2.22 (s, 3H), 2.4 (t, 4H), 2.46 (t, 2H), 3.22 (t, 4H), 3.82 (t, 4H), 3.9 (s, 3H), 4.13 (t, 2H), 7.11 (d, 1H), 7.2 (m, 1H), 7.23 (d, 1H), 7.4 (t, 1H), 7.42 (s, 1H), 7.5 (s, 1H), 7.61 (d, 2H), 7.65 (m, 1H), 7.82 (d, 1H), 9.81 (s, 1H), 10.17 (s, 1H); Mass M+H 587.

zz) The reactants were heated to 100°C for 24 hours. The product gave the following data : NMR ($DMSOd_6$) 1.82 (t, 2H), 2.15 (s, 3H), 2.19 (s, 3H), 2.38 (m, 10H), 3.19 (t, 4H),

3.77 (t, 4H), 3.82 (s, 4H), 4.03 (t, 2H), 7.05 (d, 1H), 7.1 (m, 1H), 7.17 (m, 1H), 7.37 (m, 2H), 7.41 (s, 1H), 7.57 (m,3H), 7.78 (s, 1H), 9.75 (s, 1H), 10.1 (s, 1H); Mass M+H 602.

aaa) The reactants were heated to 100°C for 24 hours. The product gave the following data : NMR ($DMSOd_6$) 1.52 (m, 1H), 1.73 (m, 2H), 2.02 (m,2H), 2.15 (s, 3H), 2.22 (s, 3H), 2.45 (m, 2H), 2.56 (m, 2H), 3.16 (t, 4H), 3.75 (t, 4H), 3.82 (s, 3H), 4.07 (t, 2H), 7.05 (d, 1H), 7.12 (m, 1H), 7.18 (d, 1H), 7.33 (m,2H), 7.37 (s, 1H), 7.48 (s, 1H), 7.52 (d, 1H), 7.57 (d, 1H), 7.78 (s, 1H), 9.72 (s, 1H), 10.08 (s, 1H); Mass M+H 573.

bbb) The reactants were heated to 100°C for 24 hours. The product gave the following data : NMR ($DMSOd_6$) 1.1 (m, 1H), 1.44 (m, 1H), 1.63 (m, 2H),1.93 (m, 3H), 2.18 (s, 3H), 2.19 (s, 3H), 2.6 (m, 1H), 2.81 (m, 1H), 3.18 (t, 4H), 3.78 (t, 4H), 3.82 (s, 3H), 3.91 (m, 2H), 7.03 (d, 1H), 7.12 (m, 1H), 7.2 (d, 1H), 7.37 (t, 1H), 7.38 (s, 1H), 7.42 (s, 1H), 7.57 (s, 2H), 7.6 (t, 1H), 7.78 (d, 1H), 9.75 (s, 1H), 10.09 (s, 1H); Mass M+H 573.

ccc) The reactants were heated to 100°C for 24 hours. The product gave the following data : NMR ($DMSOd_6$) 0.98 (t, 6H), 2.18 (s, 3H), 2.52 (m, 4H), 2.8 (t, 2H), 3.18 (t, 4H), 3.78 (t, 4H), 3.82 (s, 3H), 4.05 (t, 2H), 7.05 (d, 1H), 7.15 (m, 1H), 7.21 (d, 1H), 7.37 (m, 2H), 7.41 (s, 1H), 7.57 (m, 3H), 7.78 (d, 1H), 9.75 (s, 1H), 10.1 (s, 1H); Mass M+H 561.

ddd) The product gave the following data : NMR ($DMSOd_6$) 0.95 (t, 6H), 1.81 (m, 2H), 2.18 (s, 3H), 2.43 (m, 6H), 3.18 (t, 4H), 3.75 (t, 4H), 3.82 (s, 3H), 4.03 (t, 2H), 7.03 (d, 1H), 7.12 (m,1H), 7.21 (d, 1H), 7.37 (m, 2H), 7.42 (s, 1H), 7.52 (s, 2H), 7.57 (m,1H), 7.76 (d, 1H), 9.75 (s, 1H), 10.1 (s, 1H); Mass M+H 575.

eee) The reactants were heated to 100°C for 24 hours. The product gave the following data : NMR ($DMSOd_6$) 0.98 (d, 12H), 2.18 (s, 3H), 2.78 (t, 2H), 3.0 (m, 2H), 3.18 (t, 4H), 3.77 (t, 4H), 3.82 (s, 3H), 3.93 (t, 2H), 7.05 (d, 1H), 7.13 (m, 1H), 7.2 (d, 1H), 7.35 (t, 1H), 7.37 (s, 1H), 7.42 (s, 1H), 7.58 (m, 3H), 7.78 (d, 1H), 9.75 (s, 1H), 10.08 (s, 1H); Mass M+H 589.

fff) The reactants were heated to 100°C for 24 hours. The product gave the following data : NMR ($DMSOd_6$) 2.19 (s, 3H), 2.63 (s, 3H), 3.18 (t, 4H), 3.76 (t, 4H), 3.82 (s, 3H), 5.17 (s, 2H), 7.11 (d, 1H), 7.16 (m, 1H), 7.21 (d, 1H), 7.37 (m, 2H), 7.42 (s, 1H), 7.5 (s, 1H), 7.57 (m, 1H), 7.62 (m, 1H), 7.7 (d, 1H), 7.78 (d, 1H), 9.75 (s, 1H), 10.1 (s, 1H); Mass M+H 573.

Example 8

N-[5-(4-cyanobenzamido)-2-methylphenyl]-4-(2-methoxyethoxy)benzamide

2-Bromoethyl methyl ether (0.023 ml) was added to a suspension of N-[5-(4-cyanobenzamido)-2-methylphenyl]-4-hydroxybenzamide (0.06 g) and potassium carbonate (0.045 g) in DMF (3 ml) and the reaction mixture was stirred and heated to 80°C for 5 hours. The mixture was poured into water and extracted with ethyl acetate. The organic extract was dried ($MgSO_4$) and evaporated. The residue was triturated under diethyl ether and the resultant solid was isolated and dried under vacuum at 55°C. There was thus obtained the title compound (0.038g); NMR Spectrum: ($DMSOd_6$) 2.19 (s, 3H), 3.27 (s, 3H), 3.66 (s, 2H), 4.17 (m, 2H), 7.04 (d, 2H), 7.24 (d, 1H), 7.57 (d, 1H), 7.82 (s, 1H), 7.96 (m, 4H), 8.1 (d, 2H), 9.71 (s, 1H), 10.44 (s, 1H); Mass Spectrum: $M-H^-$ 428.

The N-[5-(4-cyanobenzamido)-2-methylphenyl]-4-hydroxybenzamide used as a starting material was obtained as follows :-

Triethylamine (23 ml) was added to a suspension of 3-nitro-4-methylaniline (10 g), 4-cyanobenzoyl chloride (13.1 g), 4-dimethylaminopyridine (0.8 g) in methylene chloride (200 ml) which had been cooled to 0°C. The reaction mixture was allowed to warm to ambient temperature and was stirred for 5 hours. The mixture was partitioned between methylene chloride and 0.5N hydrochloric acid solution. The organic phase was dried ($MgSO_4$) and evaporated and the residue was triturated under isohexane. The solid was isolated and dried under vacuum at 55°C. There was thus obtained N-(3-nitro-4-methylphenyl)-4-cyanobenzamide (18.3 g); NMR Spectrum: ($DMSOd_6$) 2.5 (s, 3H), 7.49 (d, 1H), 7.96 (m, 1H), 8.05 (d, 2H), 8.12 (d, 2H), 8.51 (d, 1H), 10.77 (s, 1H).

A solution of tin(II) chloride dihydrate (15.4 g) in concentrated hydrochloric acid (80 ml) was added to a suspension of N-(3-nitro-4-methylphenyl)-4-cyanobenzamide (6.39 g) in acetic acid (120 ml). The mixture was stirred and heated to reflux for 2 hours. The mixture was allowed to cool to ambient temperature and was basified by the addition of 2N sodium hydroxide solution. The precipitated solid was isolated and dried under vacuum at 55°C to give N-(3-amino-4-methylphenyl)-4-cyanobenzamide (5.62 g); NMR Spectrum: ($DMSOd_6$) 2.01 (s, 3H), 4.85 (s, 2H), 6.8 (d, 1H), 6.86 (d, 1H), 7.11 (s, 1H), 7.96 (d, 2H), 8.06 (d, 2H), 10.11 (s, 1H).

Oxalyl chloride (0.31 ml) was added dropwise to a solution of 4-acetoxybenzoic acid (0.54) and DMF (a few drops) in methylene chloride (25 ml) which had been cooled to 0°C. The mixture was allowed to warm to ambient temperature and was stirred for 4 hours. The mixture was evaporated and the residue was dissolved in methylene chloride (20 ml). A mixture of N-(3-amino-4-methylphenyl)-4-cyanobenzamide (0.5 g), triethylamine (0.7 ml) and 4-dimethylaminopyridine (0.024 g) in methylene chloride (5 ml) was added and the reaction mixture was stirred at ambient temperature overnight. The mixture was evaporated and the residue was triturated under 2N hydrochloric acid solution. The precipitated solid was isolated, washed with a saturated aqueous solution of sodium bicarbonate and with water and dried under vacuum at 55°C. There was thus obtained N-[5-(4-cyanobenzamido)-2-methylphenyl]-4-acetoxybenzamide (0.443 g); NMR Spectrum: ($DMSOd_6$) 2.18 (s, 3H), 2.26 (s, 3H), 7.25 (m, 3H), 7.57 (d, 1H), 7.84 (s, 1H), 8.0 (m, 4H), 8.11 (d, 2H), 9.91 (s, 1H), 10.46 (s, 1H).

A mixture of the material so obtained, sodium methoxide (0.113 g) and methanol (20 ml) was stirred at ambient temperature for 4 hours. The mixture was concentrated to approximately 5 ml by evaporation under reduced pressure and acidified by the addition of 2N hydrochloric acid. The resultant solid was washed with water and dried under vacuum at 55°C to give N-[5-(4-cyanobenzamido)-2-methylphenyl]-4-hydroxybenzamide (0.32 g); NMR Spectrum: ($DMSOd_6$) 2.18 (s, 3H), 6.84 (d, 2H), 7.22 (d, 1H), 7.57 (d, 1H), 7.83 (m, 3H), 7.98 (d, 2H), 8.1 (d, 2H), 10.13 (s, 1H), 10.43 (s, 1H); Mass Spectrum: $M-H^-$ 370.

Example 9

N-[5-(4-cyanobenzamido)-2-methylphenyl]-4-(methoxycarbonylmethoxy)benzamide

Methyl bromoacetate (0.023 ml) was added to a suspension of N-[5-(4-cyanobenzamido)-2-methylphenyl]-4-hydroxybenzamide (0.06 g) and potassium carbonate (0.045 g) in DMF (3 ml) and the mixture was stirred and heated to 80°C for 5 hours. The mixture was poured into water and extracted with ethyl acetate. The organic extract was dried ($MgSO_4$) and evaporated. The residue was triturated under diethyl ether. The resultant solid was dried under vacuum at 55°C to give the title compound as a solid (0.024 g); NMR Spectrum: ($DMSOd_6$) 2.2 (s, 3H), 3.71 (s, 3H), 4.9 (s, 2H), 7.05 (d, 2H), 7.23 (d, 1H), 7.56 (d, 1H), 7.81 (s, 1H), 7.97 (m, 4H), 8.1 (d, 2H), 9.75 (s, 1H), 10.44 (s, 1H).

Example 10

N-[5-(4-cyanobenzamido)-2-methylphenyl]-4-(chloromethyl)benzamide

Triethylamine (0.55 ml) was added to a suspension of N-(3-amino-4-methylphenyl)-4-cyanobenzamide (0.40 g), 4-(chloromethyl)benzoyl chloride (0.45 g) and 4-dimethylaminopyridine (0.019 g) in methylene chloride (12 ml) and the mixture was stirred at ambient temperature for 16 hours. The mixture was evaporated and the residue was triturated with water. The resultant solid was isolated and washed in turn with 2N hydrochloric acid and a saturated aqueous sodium bicarbonate solution. The solid was dried under vacuum at 55°C to give the required starting material (0.64 g); NMR Spectrum: ($DMSOd_6$) 2.2 (s, 3H), 4.82 (s, 2H), 7.23 (d, 1H), 7.58 (m, 3H), 7.84 (s, 1H), 7.99 (m, 4H), 8.1 (d, 2H), 9.91 (s, 1H), 10.46 (s, 1H); Mass Spectrum: M-H$^-$ 402.

Example 11

N-[5-(4-cyanobenzamido)-2-methylphenyl]-3-(chloromethyl)benzamide

Using an analogous procedure to that described in Example 10, N-(3-amino-4-methylphenyl)-4-cyanobenzamide was reacted with 3-(chloromethyl)benzoyl chloride to give the title compound as a solid (0.267 g); NMR Spectrum: ($DMSOd_6$) 2.2 (s, 3H), 4.84 (s, 2H), 7.25 (d, 1H), 7.55 (m, 2H), 7.64 (m, 1H), 7.83 (s, 1H), 7.99 (m, 4H), 8.1 (d, 2H), 9.97 (s, 1H), 10.46 (s, 1H); Mass Spectrum: M-H$^-$ 402.

Example 12

N-[5-(4-cyanobenzamido)-2-methylphenyl]-4-(diethylaminomethyl)benzamide

Diethylamine hydrochloride (0.024 g) was added to a stirred mixture of N-[5-(4-cyanobenzamido)-2-methylphenyl]-4-(chloromethyl)benzamide (0.06 g), potassium carbonate (0.082 g) and acetone (5 ml) and the reaction mixture was stirred and heated to 55°C for 16 hours. Further portions of diethylamine hydrochloride and potassium carbonate (same quanities as before) were added and the mixture was heated to 55°C for a further 4 days. The reaction mixture was evaporated and the residue was triturated with water. The solid was isolated and dried under vacuum at 55°C to give the title compound as a solid (0.044 g); NMR Spectrum: ($CDCl_3$) 1.06 (t, 6H), 2.28 (s, 3H), 2.53 (m, 4H), 3.63 (s, 2H), 7.2

(d, 1H), 7.5 (d, 2H), 7.74 (m, 4H), 7.81 (d, 2H), 7.97 (d, 2H), 8.15 (s, 1H), 8.27 (s, 1H); Mass Spectrum: M-H$^-$ 439.

Example 13

N-[5-(4-cyanobenzamido)-2-methylphenyl]-4-(2-methoxyethylaminomethyl)benzamide

2-Methoxyethylamine (0.019 ml) was added to a stirred solution of N-[5-(4-cyanobenzamido)-2-methylphenyl]-4-(chloromethyl)benzamide (0.060 g) and potassium carbonate (0.041 g) in acetone (5 ml) and the reaction mixture was heated to 55°C overnight. Further portions of 2-methoxyethylamine and potassium carbonate (same quantities as before) were added and the reaction mixture was stirred at 55°C for a further 4 days. The reaction mixture was evaporated and the residue was triturated with water. The resultant solid was isolated and dried under vacuum at 55°C to give the title compound as a solid (0.039 g, 59%); NMR Spectrum: ($CDCl_3$) 2.27 (s, 3H), 2.83 (m, 2H), 3.37 (m, 4H), 3.56 (t, 2H), 3.91 (s, 2H), 7.19 (d, 1H), 7.49 (d, 2H), 7.77 (m, 7H), 7.95 (d, 2H), 8.13 (s, 1H), 8.3 (s, 1H); Mass Spectrum: M-H$^-$ 441.

Example 14

N-[5-(4-cyanobenzamido)-2-methylphenyl]-4-(2-ethoxyethoxy)benzamide

Phosphoryl chloride (0.03 ml) was added dropwise to a stirred mixture of N-(3-amino-4-chlorophenyl)-4-cyanobenzamide (0.08 g), 4-(2-ethoxyethoxy)benzoic acid (J. Org. Chem., 1973, 38, 3160; 0.062 g) and pyridine (4 ml) which had been cooled to -15°C. The reaction mixture was stirred at -15°C for 3 hours and then allowed to warm to ambient temperature. The mixture was stirred for 48 hours. The reaction mixture was diluted with water and stirred overnight. The precipitate was isolated, washed with diethyl ether and dried under vacuum at 55°C to give the title compound (0.024 g); NMR Spectrum: ($DMSOd_6$) 1.15 (t, 3H), 3.49 (m, 2H), 3.73 (m, 2H), 4.19 (m, 2H), 9.86 (s, 1H), 10.62 (s, 1H); Mass Spectrum: M-H$^-$ 462.

Example 15

N-[2-chloro-5-(4-cyanobenzamido)phenyl]-4-[2-(imidazol-1-yl)ethoxy]benzamide

Using an analogous procedure to that described in Example 14, N-(3-amino-4-chlorophenyl)-4-cyanobenzamide was reacted with 4-[2-(imidazol-1-yl)ethoxy]benzoic acid (J. Med. Chem., 1985, 28, 1427) to give the title compound in 75% yield; NMR Spectrum: ($DMSOd_6$) 4.48 (t, 2H), 4.65 (m, 2H), 7.09 (d, 1H), 7.51 (d, 1H), 7.68 (m, 3H), 7.82 (s, 1H), 8.0 (m, 4H), 8.1 (m, 2H), 8.73 (d, 1H), 9.18 (s, 1H), 9.89 (s, 1H), 10.66 (s, 1H); Mass Spectrum: $M-H^-$ 484.

The N-(3-amino-4-chlorophenyl)-4-cyanobenzamide used as a starting material was obtained as follows :-

4-Cyanobenzoyl chloride (11.92 g) was added slowly to a stirred solution of 4-chloro-3-nitroaniline (10.4 g) in pyridine (20 ml) and the mixture was stirred and heated to 115°C for 18 hours. The mixture was cooled to ambient temperature and poured into water (150 ml) and stirred for 30 minutes. The resultant precipitate was isolated, washed with water and dried to give N-(4-chloro-3-nitrophenyl)-4-cyanobenzamide (18 g), m.p. 213°C; NMR Spectrum: ($DMSOd_6$) 7.78 (d, 1H), 8.05 (m, 3H), 8.1 (d, 2H), 8.58 (s, 1H), 10.93 (s, 1H).

A portion (3.6 g) of the material so obtained was added to a stirred suspension of iron powder (10 g) in a mixture of ethanol (130 ml), water (30 ml) and glacial acetic acid (4 ml). The mixture was heated to 75°C for 1 hour and thereafter, whilst hot, basified by the addition of sodium carbonate. The mixture was filtered and the filtrate was evaporated. The resultant solid was stirred in water for 3 hours. The solid was isolated and dried to give the required starting material (2.7 g), m.p. 237.7°C; NMR Spectrum: ($DMSOd_6$) 5.44 (s, 2H), 6.98 (m, 1H), 7.21 (d, 1H), 7.42 (d, 1H), 8.07 (d, 2H), 8.14 (d, 2H), 10.36 (s, 1H).

Example 16

N-[5-(3-dimethyaminobenzamido)-2-methylphenyl]-4-(2-ethoxyethoxy)benzamide

Oxalyl chloride (0.087 ml) was added dropwise to a stirred solution of 4-(2-ethoxyethoxy)benzoic acid (J. Org. Chem., 1973, 38, 3160; 0.21 g) and DMF (a few drops) which had been cooled to 0°C The mixture was allowed to warm to ambient temperature and was stirred for five hours. The resultant solution was evaporated to dryness

and the residue was dissolved in methylene chloride (10 ml). N-(3-Amino-4-methylphenyl)-3-dimethylaminobenzamide (0.135 g) and triethylamine (0.189 ml) were added in turn and the mixture was stirred at ambient temperature for 16 hours. The resultant solution was washed with a saturated aqueous solution of sodium bicarbonate and with brine, dried ($MgSO_4$) and evaporated. The residue was triturated under a mixture of ethyl acetate and diethyl ether. The resulting solid was isolated and dried under vacuum at 40°C to give the title compound (0.164 g); NMR Spectrum: ($DMSOd_6$) 1.1 (m, 3H), 2.18 (s, 3H), 2.97 (s, 6H), 3.5 (m, 2H), 3.7 (m, 2H), 4.16 (m, 2H), 7.02 (m, 3H), 7.2 (d, 1H), 7.34 (m, 3H), 7.59 (d, 1H), 7.79 (s, 1H), 7.95 (d, 2H), 9.74 (s, 1H), 10.12 (s, 1H); Mass Spectrum: $M+H^+$ 462.

Example 17

N-[2-chloro-5-(4-cyanobenzamido)phenyl]-3-(1-methylpiperidin-4-yloxy)benzamide

Oxalyl chloride (0.11 ml) was added to a stirred suspension of 3-(1-methylpiperidin-4-yloxy)benzoic acid (0.246 g) in methylene chloride (10 ml) which had been cooled to 0°C. DMF (1 drop) was added and the mixture was stirred for 16 hours and allowed to warm to ambient temperature. The solvent was evaporated to give an orange coloured solid. The acid chloride so obtained was added to a mixture of N-(3-amino-4-chlorophenyl)-4-cyanobenzamide (0.255 g) and pyridine (3 ml) and the reaction mixture was stirred and heated to 100°C for 12 hours. After cooling, the pyridine was evaporated and water (25 ml) added. The aqueous phase was extracted with ethyl acetate and the organic phase was dried ($MgSO_4$) and evaporated. The residual oil was purified by column chromatography on silica gel using a 9:1 mixture of ethyl acetate and methanol as eluent. There was thus obtained the title compound as a solid (0.031 g), m.p. 177-179°C; Mass Spectrum: $M+H^+$ 489.

The 3-(1-methylpiperidin-4-yloxy)benzoic acid starting material was prepared as follows :-

Diethyl azodicarboxylate (2.3 ml) was added dropwise to a stirred suspension of triphenylphosphine (3.9 g), ethyl 3-hydroxybenzoate (2.3 g) and 4-hydroxy-1-methylpiperidine (1.15 g) in THF (40 ml) which had been cooled to 5°C. The mixture was allowed to warm to ambient temperature and stirred for 18 hours. The solvent was evaporated and the residue was dissolved in ethyl acetate. The organic phase was extracted with 2N

hydrochloric acid. The aqueous extract was washed with ethyl acetate, basified with potassium carbonate and extracted with ethyl acetate. The resultant organic phase was dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography on silica gel using a 49:1 mixture of methylene chloride and methanol as eluent. There was thus obtained ethyl 3-(1-methylpiperidin-4-yloxy)benzoate (0.552 g) as an oil; NMR Spectrum : ($DMSOd_6$) 1.33 (t, 3H), 1.78 (m, 2H), 1.95 (m, 2H), 2.23 (m, 5H), 2.62 (m, 2H), 4.32 (m, 3H), 7.02 (m, 1H), 7.24 (t, 1H), 7.52 (d, 1H), 7.55 (d, 1H).

The material so obtained was dissolved in a mixture of ethanol (5 ml) and water (0.5 ml) containing sodium hydroxide (0.16 g). The mixture was stirred and heated to 50°C for 1 hour and then stored at ambient temperature for 18 hours. The mixture was evaporated. A 1N hydrochloric acid solution (4 ml) was added and the mixture was re-evaporated. The residue was washed with methylene chloride and dried. There was thus obtained 3-(1-methylpiperidin-4-yloxy)benzoic acid (0.265 g) as a solid; NMR Spectrum: ($DMSOd_6$) 1.7 (m, 2H), 1.96 (m, 2H), 2.34 (s, 3H), 2.46 (m, 2H), 7.17 (m, 1H), 7.37 (t, 1H), 7.42 (d, 1H), 7.5 (d, 1H).

Example 18

N-[5-(3-carboxymethoxybenzamido)-2-methylphenyl]-3,4-dimethoxybenzamide

Trifluoroacetic acid (5 ml) was added to a stirred solution of N-[5-(3-tert-butoxycarbonylmethoxybenzamido)-2-methylphenyl]-3,4-dimethoxybenzamide (0.455 g) in methylene chloride (5 ml) and the mixture was stirred at ambient temperature for 1 hour. The mixture was evaporated and the residue was azeotroped with toluene. The resultant solid was dried under vacuum at 60°C. There was thus obtained the title compound (0.375 g), m.p. 206-207°C; NMR Spectrum: ($DMSOd_6$) 2.18 (s, 3H), 3.83 (s, 6H), 4.74 (s, 2H), 7.06 (d, 1H), 7.11 (m, 1H), 7.23 (d, 1H), 7.43 (t, 1H), 7.48 (d, 1H), 7.55 (br m, 1H), 7.63 (m, 1H), 7.8 (d, 1H), 9.75 (br s, 1H), 10.17 (br s, 1H); Mass Spectrum: $M+H^+$ 465.

Example 19

N-{5-[4-(3-hydroxypropoxy)benzamido]-2-methylphenyl}-3,4-dimethoxybenzamide

S,S-Dioxothiamorpholine trifluoroacetic acid salt (0.22 g) was added to a stirred mixture of N-{5-[4-(3-chloropropoxy)benzamido]-2-methylphenyl}-3,4-dimethoxybenzamide

(0.5 g), tetra-n-butylammonium iodide (0.096 g), di-isopropylethylamine (0.29 g) and DMA (4 ml) and the mixture was stirred and heated to 100°C for 1 week. The reaction mixture was allowed to cool to ambient temperature and poured into water (100 ml). The resultant precipitate was isolated and washed with water and with diethyl ether. The solid so obtained was purified by column chromatography on silica gel using increasingly polar mixtures of methylene chloride and methanol as eluent. There were thus obtained in turn :-

(a) a foam which was dried under vacuum at 60°C to give the title compound (0.146 g); NMR Spectrum: ($DMSOd_6$+CD_3CO_2D) 1.86 (m, 2H), 2.19 (s, 3H), 3.55 (t, 2H), 3.82 (s, 6H), 4.11 (t, 2H), 7.03 (d, 2H), 7.06 (d, 1H), 7.2 (d, 1H), 7.56 (m, 2H), 7.62 (m, 1H), 7.79 (d, 1H), 7.94 (d, 2H), 9.75 (br s, 1H), 10.03 (br s, 1H); Mass Spectrum: $M+H^+$ 465; Elemental Analysis: Found C, 66.3; H, 5.9; N, 6.0;
$C_{26}H_{28}N_2O_6$ $0.5H_2O$ requires C, 66.0; H, 6.1; N, 5.9%; and

(b) a glassy brown solid which was dried under vacuum at 60°C to give N-{5-[4-(3-(S,S-dioxothiamorpholin-1-yl)propoxy)benzamido]-2-methylphenyl}-3,4-dimethoxybenzamide (0.057 g); NMR Spectrum: ($DMSOd_6$) 1.86 (m, 2H), 2.17 (s, 3H), 2.62 (t, 2H), 2.88 (m, 4H), 3.05 (m, 4H), 3.83 (s, 6H), 4.09 (t, 2H), 7.03 (d, 2H), 7.06 (d, 1H), 7.21 (d, 1H), 7.54 (m, 2H), 7.62 (m, 1H), 7.8 (d, 1H), 7.93 (d, 2H), 9.73 (br s, 1H), 10.03 (br s, 1H); Mass Spectrum: $M+H^+$ 582.

Example 20

N-{5-[4-(N-(3-dimethylaminopropyl)-N-methylamino)benzamido]-2-methylphenyl}-3,4-dimethoxybenzamide

N-(3-Dimethylaminopropyl)-N-methylamine (0.325 g) was added to a stirred mixture of N-[5-(4-fluorobenzamido)-2-methylphenyl]-3,4-dimethoxybenzamide (0.38 g), potassium carbonate (0.39 g) and DMSO (5 ml). The mixture was stirred and heated to 130°C for 10 days. The mixture was allowed to cool to ambient temperature and partitioned between ethyl acetate and water. The organic phase was washed with water, dried ($MgSO_4$) and evaporated to give an oil which was purified by column chromatography on silica gel using increasingly polar mixtures of methylene chloride and methanol as eluent. The material so obtained was triturated under diethyl ether and the resultant solid was dried under vacuum at 60°C. There was thus obtained the title compound (0.16 g), m.p. 164-165°C;

NMR Spectrum: ($DMSOd_6$) 1.6 (m, 2H), 2.16 (s, 3H), 2.2 (s, 6H), 2.3 (t, 2H), 2.94 (s, 3H), 3.4 (t, 2H), 3.83 (s, 6H), 6.72 (d, 2H), 7.06 (d, 1H), 7.18 (d, 1H), 7.55 (m, 2H), 7.63 (m, 1H), 7.79 (d, 2H), 7.84 (d, 2H), 9.71 (br s, 1H), 9.8 (br s, 1H); Mass Spectrum: $M+H^+$ 505; Elemental Analysis: Found C, 65.9; H, 7.0; N, 10.4; $C_{29}H_{36}N_4O_4$ $1.3H_2O$ requires C, 66.0; H, 7.4; N, 10.6%.

The N-[5-(4-fluorobenzamido)-2-methylphenyl]-3,4-dimethoxybenzamide used as a starting material was obtained as follows :-

Using an analogous procedure to that described in Example 3, N-(5-amino-2-methylphenyl)-3,4-dimethoxybenzamide was reacted with 4-fluorobenzoyl chloride. There was thus obtained the required starting material, m.p. 210-211°C; NMR Spectrum: ($DMSOd_6$) 2.18 (s, 3H), 3.83 (s, 6H), 7.07 (d, 1H), 7.23 (d, 1H), 7.35 (t, 2H), 7.55 (m, 2H), 7.57 (d, 1H), 7.63 (m, 1H), 7.8 (d, 1H), 8.03 (m, 2H), 9.75 (br s, 1H), 10.39 (br s, 1H).

Example 21

N-[5-(3-chloromethylbenzamido)-2-methylphenyl]-3,4-dimethoxybenzamide

Using an analogous procedure to that described in Example 2, N-(5-amino-2-methylphenyl)-3,4-dimethoxybenzamide was reacted with 3-(chloromethyl)benzoyl chloride to give the title compound in 87% yield; NMR Spectrum: ($DMSOd_6$) 2.19 (s, 3H), 3.82 (s, 6H), 4.84 (s, 2H), 7.06 (d, 1H), 7.23 (d, 1H), 7.57 (m, 5H), 7.80 (s, 1H), 7.9 (d, 1H), 8.0 (s, 1H), 9.76 (s, 1H), 10.26 (s, 1H); Mass Spectrum: $M+H^+$ 439.

Example 22

N-[2-Methyl-5-(3-trifluoromethylbenzamido)phenyl]-4-(2-ethoxyethoxy)benzamide

A solution of N-(5-amino-2-methylphenyl)-4-(2-ethoxyethoxy)benzamide (0.141 g) and triethylamine (0.121 g) in methylene chloride (5 ml) was added to 3-trifluoromethylbenzoyl chloride (0.104 g) and the resultant mixture was stirred at ambient temperature for 18 hours. The mixture was washed in turn with a 1M aqueous citric acid solution, a saturated aqueous sodium bicarbonate solution and water. The organic solution was evaporated and the residue was triturated under a mixture of diethyl ether and ethyl acetate. The resultant solid was isolated and dried under vacuum. There was thus obtained the title compound (weight 0.042 g) ; Mass Spectrum: $M+H^+$ 487.

The N-(5-amino-2-methylphenyl)-4-(2-ethoxyethoxy)benzamide used as a starting material was obtained as follows :-

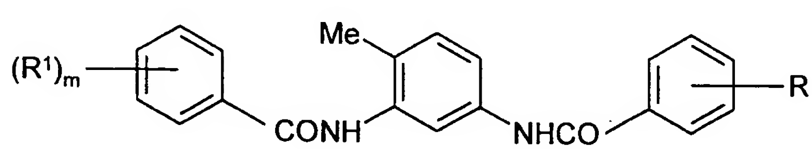
Oxalyl chloride (2.7 ml) was added to a mixture of 4-(2-ethoxyethoxy)benzoic acid (5.25 g) and DMF (1 ml) in methylene chloride (100 ml) and the reaction mixture was stirred at ambient temperature for 4 hours. The mixture was evaporated and the residue was dissolved in methylene chloride (100 ml). 2-Methyl-5-nitroaniline (3.17 g), 4-dimethylaminopyridine (0.254 g) and triethylamine (7.3 ml) were added in turn and the resultant reaction mixture was stirred at ambient temperature for 16 hours. The mixture was evaporated and the residue was partitioned between ethyl acetate and water. The organic phase was dried and evaporated to give N-(2-methyl-5-nitrophenyl)-4-(2-ethoxyethoxy)benzamide as an oil which was used without further purification.

10% Palladium-on-carbon catalyst (0.72 g) was added to a solution of the material so obtained in methanol (300 ml). Ammonium formate (13.1 g) was added and the reaction mixture was stirred and heated to reflux for 1.75 hours. The mixture was filtered and the filtrate was evaporated. The residue was triturated under water and the resultant solid was isolated and dried under vacuum at 55°C. The solid so obtained was dissolved in the minimum amount of hot methanol and precipitated by the addition of water. There was thus obtained the required starting material as a solid (4.33 g); Mass Spectrum: $M+H^+$ 278.

Example 23

Using an analogous procedure to that described in Example 22, the appropriate benzoyl chloride was reacted with N-(5-amino-2-methylphenyl)benzamide to give the compounds described in Table III.

Table III



No.	$(R^1)_m$	R	Note
1	4-(2-ethoxyethoxy)	hydrogen	a
2	4-(2-ethoxyethoxy)	2-fluoro	b
3	4-(2-ethoxyethoxy)	4-chloro	c
4	4-(2-ethoxyethoxy)	3,4-chloro	d
5	4-(2-ethoxyethoxy)	4-cyano	e
6	4-(2-ethoxyethoxy)	2-methoxy	f
7	4-(2-ethoxyethoxy)	3-ethoxy	g
8	4-(2-ethoxyethoxy)	4-ethyl	h
9	4-(2-ethoxyethoxy)	4-propyl	i
10	4-diethylaminomethyl	hydrogen	j
11	4-diethylaminomethyl	2-fluoro	k
12	4-diethylaminomethyl	4-fluoro	l
13	4-diethylaminomethyl	3-chloro	m
14	4-diethylaminomethyl	2,4-dichloro	n
15	4-diethylaminomethyl	3,4-dichloro	o
16	4-diethylaminomethyl	3-trifluoromethyl	p
17	4-diethylaminomethyl	4-methoxycarbonyl	q
18	4-diethylaminomethyl	3-cyano	r
19	4-diethylaminomethyl	4-methoxy	s
20	4-diethylaminomethyl	3-ethoxy	t
21	4-diethylaminomethyl	3,4-dimethoxy	u
22	4-diethylaminomethyl	3-morpholino	v
23	4-diethylaminomethyl	3-trifluoromethoxy	w
24	4-diethylaminomethyl	3-phenoxy	x
25	4-diethylaminomethyl	3-bromo	y
26	3-(4-methylpiperazin-1-ylmethyl)	3-trifluoromethoxy	z
27	3-(4-methylpiperazin-1-ylmethyl)	4-trifluoromethoxy	aa
28	3-(4-methylpiperazin-1-ylmethyl)	3-phenoxy	bb

Notes

a) The product gave the following data : Mass M+H 419.

b) The product gave the following data : Mass M+H 437.

c) The product gave the following data : Mass M+H 453.

d) The product gave the following data : Mass M+H 487.

e) The product gave the following data : Mass M+H 444.

f) The product gave the following data : Mass M+H 449.

g) The product gave the following data : Mass M+H 464.

h) The product gave the following data : Mass M+H 447.

i) The product gave the following data : Mass M+H 461.

j) The step of washing the reaction mixture with a 1M aqueous citric acid solution was omitted. The product gave the following data : Mass M+H 416.

The N-(5-amino-2-methylphenyl)-4-diethylaminomethylbenzamide used as a starting material was prepared as follows :-

4-Chloromethylbenzoyl chloride (21.4 g) was added to a stirred mixture of 2-methyl-5-nitroaniline (26.6 g), triethylamine (31.5 ml) and methylene chloride (600 ml) and the resultant mixture was stirred at ambient temperature for 16 hours. The precipitate was isolated, washed in turn with 1N aqueous hydrochloric acid solution and with diethyl ether and dried under vacuum at 40°C. There was thus obtained N-(2-methyl-5-nitrophenyl)-4-chloromethylbenzamide (18 g); NMR ($DMSOd_6$) 2.38 (s, 3H), 4.83 (s, 2H), 7.54-7.61 (m, 3H), 7.98-8.02 (m, 3H), 8.34 (s, 1H), 10.15 (s, 1H); Mass M+H 305.

Diethylammonium chloride(64.2 g) was added to a stirred suspension of the material so obtained and potassium carbonate (18.2 g) in acetone (750 ml). The mixture was stirred and heated to 54°C for 16 hours. The resultant mixture was evaporated and the residue was dissolved in methylene chloride. The organic solution was washed with water and evaporated. The resultant solid was isolated and dried under vacuum at 40°C. There was thus obtained N-(2-methyl-5-nitrophenyl)-4-diethylaminomethylbenzamide (18.1 g); NMR ($DMSOd_6$) 0.97 (t, 6H), 2.36 (s, 3H), 2.44-2.49 (m, 4H), 3.58 (s, 2H), 7.43 (d, 2H), 7.51 (d, 1H), 7.94 (s, 3H), 8.38 (s, 1H); Mass M+H 342.

Iron powder (29.5 g) was added to a stirred suspension of the material so obtained in

ethanol (500 ml), water (50 ml) and acetic acid (10 ml). The mixture was heated to reflux and stirred for 5 hours. Water (50 ml) was added and the mixture was basified by the addition of sodium carbonate. The mixture was filtered and the filtrate was evaporated. The residue was triturated under water. The resultant solid was isolated, washed with diethyl ether and dried under vacuum at 40°C. There was thus obtained the required starting material (18 g); NMR ($DMSOd_6$) 0.97 (t, 6H), 2.02 (s, 3H), 2.44-2.49 (m, 4H), 3.56 (s, 2H), 6.37 (d, 1H), 7.59 (s, 1H), 6.85 (d, 1H), 7.41 (d, 2H), 7.87 (d, 2H), 9.53 (s, 1H); Mass M+H 312.

k) The step of washing the reaction mixture with a 1M aqueous citric acid solution was omitted. The product gave the following data : Mass M+H 434.

l) The step of washing the reaction mixture with a 1M aqueous citric acid solution was omitted. The product gave the following data : Mass M+H 434.

m) The step of washing the reaction mixture with a 1M aqueous citric acid solution was omitted. The product gave the following data : Mass M+H 450.

n) The step of washing the reaction mixture with a 1M aqueous citric acid solution was omitted. The product gave the following data : Mass M+H 485.

o) The step of washing the reaction mixture with a 1M aqueous citric acid solution was omitted. The product gave the following data : Mass M+H 485.

p) The step of washing the reaction mixture with a 1M aqueous citric acid solution was omitted. The product gave the following data : Mass M+H 484.

q) The step of washing the reaction mixture with a 1M aqueous citric acid solution was omitted. The product gave the following data : Mass M+H 474.

r) The step of washing the reaction mixture with a 1M aqueous citric acid solution was omitted. The product gave the following data : Mass M+H 441.

s) The step of washing the reaction mixture with a 1M aqueous citric acid solution was omitted. The product gave the following data : Mass M+H 446.

t) The step of washing the reaction mixture with a 1M aqueous citric acid solution was omitted. The product gave the following data : Mass M+H 460.

u) The step of washing the reaction mixture with a 1M aqueous citric acid solution was omitted. The product gave the following data : Mass M+H 476.

v) The step of washing the reaction mixture with a 1M aqueous citric acid solution was omitted. Trituration of the reaction product did not provide a solid. The organic mixture was evaporated and the residue was purified by column chromatography on an ion exchange column (isolute SCX column from International Sorbent Technology Limited, Hengoed, Mid-Glamorgan, UK) using a 99:1 mixture of methanol and a saturated aqueous ammonium hydroxide solution as eluent. The product gave the following data : NMR: ($DMSOd_6$) 1.0 (t, 6H), 2.19 (s, 3H), 2.44-2.49 (m, 4H), 3.15-3.18 (m, 4H), 3.58 (s, 2H), 3.70-3.76 (m, 4H), 7.08-7.15 (m, 1H), 7.2 (d, 1H), 7.32-7.38 (m, 2H), 7.44-7.48 (m, 3H), 7.53-7.6 (m, 1H), 7.90-7.94 (m, 2H), 9.82 (s, 1H), 10.11 (s, 1H); Mass: M+H 501.

w) The product was deposited as a precipitate during the 18 hour reaction period. The precipitate was isolated and washed with methylene chloride. The product gave the following data : Mass M+H 500.

x) The step of washing the reaction mixture with a 1M aqueous citric acid solution was omitted. The product gave the following data : Mass M+H 508.

The 3-phenoxybenzoyl chloride used as a starting material was prepared as follows :-

Oxalyl chloride (0.11 ml) was added dropwise to a stirred mixture of 3-phenoxybenzoic acid (0.214 g), DMF (a few drops) and methylene chloride (4 ml) which had been cooled to 0°C. The mixture was stirred at ambient temperature 24 hours. The solvent was evaporated to give the required acid chloride which was used without further purification.

y) The step of washing the reaction mixture with a 1M aqueous citric acid solution was omitted. The product gave the following data : Mass M+H 494.

z) The step of washing the reaction mixture with a 1M aqueous citric acid solution was omitted. The product gave the following data : Mass M+H 527.

The N-(5-amino-2-methylphenyl)-3-(4-methylpiperazin-1-ylmethyl)benzamide used as a starting material was prepared as follows :-

3-Chloromethylbenzoyl chloride (24.8 ml) was added to a stirred mixture of 2-methyl-5-nitroaniline (26.6 g), triethylamine (49 ml) and methylene chloride (800 ml) and the mixture was stirred at ambient temperature for 16 hours. The

precipitate was isolated, washed with 1N aqueous hydrochloric acid solution and with diethyl ether and dried under vacuum at 40°C. There was thus obtained 3-chloromethyl-N-(2-methyl-5-nitrophenyl)-benzamide (43.5 g); NMR ($DMSOd_6$) 2.38 (s, 3H), 2.85 (s, 2H), 7.53-7.58 (m, 2H), 7.67 (d, 1H), 7.95(d, 1H), 8.01-8.04 (m, 2H), 8.32 (s, 1H), 10.19 (s, 1H); Mass M+H 305.

1-Methylpiperazine (8.03 ml) was added to a stirred mixture of a portion (20 g) of the material so obtained, potassium carbonate (18.2 g) and acetone (750 ml) and the mixture was heated to 54°C and stirred for 16 hours. The resultant solution was evaporated and the residue was dissolved in methylene chloride. The organic solution was washed with water and evaporated. There was thus obtained N-(2-methyl-5-nitrophenyl)-3-(4-methylpiperazin-1-ylmethyl)benzamide (26.4 g); NMR ($DMSOd_6$) 2.06 (s, 3H), 2.12 (s, 3H), 2.31-2.37 (m, 8H), 3.52 (s, 2H), 7.48-7.57 (m, 3H), 7.87 (d, 2H), 8.01 (m, 1H), 8.33 (s, 1H); Mass M+H 369.

Iron powder was added to a stirred mixture of a portion (18.0 g) of the material so obtained, ethanol (500 ml), water (50 ml) and acetic acid (10 ml). The resultant mixture was stirred and heated to reflux for 5 hours. Water (50 ml) was added and the mixture was basified by the addition of sodium carbonate. The mixture was filtered and the filtrate was evaporated to dryness. The residue was triturated under water and the resultant solid was isolated and dried under vacuum at 40°C. There was thus obtained N-(5-amino-2-methylphenyl)-3-(4-methylpiperazin-1-ylmethyl)benzamide (11.1 g); NMR ($DMSOd_6$) 2.03 (s, 3H), 2.13 (s, 3H), 2.24-2.4 (m, 8H), 3.5 (s, 2H), 4.86 (s, 2H) 6.35 (d, 1H), 6.57 (s, 1H), 6.86 (d, 1H), 7.40-7.48 (m, 2H), 7.78-7.83 (m, 2H), 9.57 (s, 1H); Mass M+H 339.

aa) The step of washing the reaction mixture with a 1M aqueous citric acid solution was omitted. The product gave the following data : Mass M+H 527.

bb) The step of washing the reaction mixture with a 1M aqueous citric acid solution was omitted. The product gave the following data : Mass M+H 535.

Example 24

N-[2-Methyl-5-(2-naphthoylamino)phenyl]-4-(2-ethoxyethoxy)benzamide

Using an analogous procedure to that described in Example 22, 2-naphthoyl chloride was reacted with N-(5-amino-2-methylphenyl)-4-(2-ethoxyethoxy)benzamide to give the title compound in 23% yield; Mass Spectrum: $M+H^+$ 470.

Example 25

N-[2-methyl-5-(3-morpholinobenzamido)phenyl]-3-piperidin-4-yloxybenzamide

1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.23 g) was added to a stirred mixture of 3-(1-tert-butoxycarbonylpiperidin-4-yloxy)benzoic acid (0.321 g), N-(3-amino-4-methylphenyl)-3-morpholinobenzamide (0.311 g), 1-hydroxybenzotriazole (0.202 g) and DMF (5 ml) which had been cooled to 0°C. The reaction mixture was allowed to come to ambient temperature and was stirred for 16 hours. The reaction mixture was partitioned between ethyl acetate and water. The organic phase was washed with water, and with a saturated aqueous sodium bicarbonate solution, dried ($MgSO_4$) and evaporated. There was thus obtained N-[2-methyl-5-(3-morpholinobenzamido)phenyl]-3-(1-tert-butoxycarbonylpiperidin-4-yloxy)benzamide (0.307 g); NMR Spectrum: ($DMSOd_6$) 1.36 (s, 9H), 1.53 (m, 2H), 1.92 (m, 2H), 2.16 (s, 3H), 3.18 (t, 4H), 3.22 (m, 2H), 3.62 (m, 2H), 3.75 (t, 4H), 4.62 (m, 1H), 7.18 (m, 3H), 7.37 (m, 2H), 7.41 (m, 2H), 7.52 (s, 1H), 7.58 (m, 2H), 7.78 (d, 1H), 9.84 (s, 1H), 10.13 (s, 1H); Mass Spectrum: $M+H^+$ 615.

Trifluoroacetic acid (0.80 ml) was added to a stirred solution of the material so obtained in methylene chloride (10 ml) which had been cooled to 0°C. The reaction mixture was stirred at ambient temperature for 18 hours. The mixture was evaporated and the residue was triturated under ethyl acetate to give the title compound, as its trifluoroacetate salt, (0.162 g); NMR Spectrum: ($DMSOd_6$) 1.9 (m, 2H), 2.12 (m, 2H), 2.19 (s, 3H), 3.05 (m, 2H), 3.15 (t, 4H), 3.5 (m, 2H), 3.78 (t, 4H), 4.78 (m, 1H), 7.12 (m, 1H), 7.21 (d, 2H), 7.38 (m, 4H), 7.57 (m, 3H), 7.8 (s, 1H), 9.02 (m, 2H), 9.9 (s, 1H), 10.15 (s, 1H); Mass Spectrum: $M+H^+$ 515.

The solid so obtained was dissolved in water (5 ml) and basified by the addition of potassium carbonate. The resultant precipitate was collected and dried under vacuum to give the title compound (0.07 g), m.p. 162-166°C; Mass Spectrum: $M+H^+$ 515.

The 3-(1-tert-butoxycarbonylpiperidin-4-yloxy)benzoic acid used as a starting material was obtained as follows :-

N-tert-Butoxycarbonyl-4-hydroxypiperidine was obtained from a commercial source, for example from Neosystem, F67100, Strasbourg, France, or was prepared by the following procedure. A solution of di-tert-butyl dicarbonate (53.9 g) in methylene chloride (100 ml) was added dropwise to a stirred mixture of 4-hydroxypiperidine (25 g), triethylamine (50 ml) and methylene chloride (250 ml) which had been cooled to 0°C. The resultant mixture was allowed to warm to ambient temperature and was stirred for 18 hours. The mixture was evaporated and the residue was purified by chromatography on silica a 2:1 mixture of isohexane and ethyl acetate as eluent. The oil so obtained was dried under vacuum at 60°C to give N-tert-butoxycarbonyl-4-hydroxypiperidine as a white solid (49.1 g); NMR Spectrum: ($DMSOd_6$) 1.39 (s, 9H), 1.55 (m, 2H), 1.78 (m, 2H), 2.95 (m, 2H), 3.76 (m, 2H).

Diethyl azodicarboxylate (1.95 ml) was added dropwise over 5 minutes to a stirred mixture of N-tert-butoxycarbonyl-4-hydroxypiperidine (2 g), ethyl 3-hydroxybenzoate (1.66 g), triphenylphosphine (3.2 g) and THF (40 ml) which had been cooled to 0°C. The mixture was stirred at ambient temperature for 40 hours. The solvent was evaporated and the residue was triturated under a 9:1 mixture (40 ml) of isohexane and ethyl acetate. The mixture was filtered and the filtrate was evaporated. The residue was purified by column chromatography on silica using a 9:1 mixture (40 ml) of isohexane and ethyl acetate as eluent. There was thus obtained ethyl 3-(1-tert-butoxycarbonylpiperidin-4-yloxy)benzoate as an oil (1.82 g); NMR Spectrum: ($CDCl_3$) 1.41 (t, 3H), 1.46 (s, 9H), 1.93 (m, 2H), 3.38 (m, 2H), 3.7 (m, 2H), 4.36 (q, 2H), 4.52 (m, 1H), 7.1 (m, 1H), 7.35 (t, 3H), 7.58 (s, 1H), 7.62 (d, 1H).

Sodium hydroxide solution (10M; 1.0 ml) was added to a solution in ethanol (10 ml) of the ester so obtained and the mixture was stirred at ambient temperature for 18 hours. The mixture was evaporated and the residue was dissolved in water (5 ml). A 1M aqueous hydrochloric acid solution (10 ml) and glacial acetic acid (1 ml) were added in turn and the mixture was extracted with methylene chloride. The organic phase was dried ($MgSO_4$) and evaporated to give the required starting material as a colourless solid (1.32 g), m.p. 148-150°C; Mass Spectrum: $M+H^+$ 322.

Example 26

N-{5-[3-(N-methylmethanesulphonylamino)benzamido]-2-methylphenyl}-3,4-dimethoxybenzamide

A solution of N-[5-(3-methanesulphonylaminobenzamido)-2-methylphenyl]-3,4-dimethoxybenzamide (0.3 g) in DMF (5 ml) was added portionwise to a stirred mixture of sodium hydride (0.025 g) in DMF (5 ml). The resultant mixture was stirred at ambient temperature for 40 minutes. Methyl iodide (0.088 g) was added and the mixture was stirred at ambient temperature for 3 hours. The mixture was poured into water (150 ml). The resultant precipitate was isolated, washed in turn with water and diethyl ether and dried under vacuum at 60°C. There was thus obtained the title compound (0.18 g); m.p. 168-169°C; NMR Spectrum: ($DMSOd_6$) 2.19 (s, 3H), 2.99 (s, 3H), 3.82 (s, 6H), 7.07 (d, 1H), 7.21 (d, 1H), 7.59 (m, 5H), 7.79 (s, 1H), 7.87 (d, 1H), 7.93 (s, 1H), 9.75 (br s, 1H), 10.25 (br s, 1H); Mass Spectrum: $M+H^+$ 498.

Example 27

N-[5-(3-dimethylaminobenzamido)-2-methylphenyl]-3-methanesulphonylaminobenzamide

Methanesulphonyl chloride (0.46 g) was added to a stirred mixture of N-[5-(3-dimethylaminobenzamido)-2-methylphenyl]-3-aminobenzamide, pyridine (0.56 ml) and methylene chloride (30 ml) and the resultant mixture was stirred at ambient temperature for 48 hours. The precipitate was isolated, washed in turn with methylene chloride and diethyl ether and dried under vacuum at 60°C. There was thus obtained the title compound (1.64 g); m.p. 239-240°C; NMR Spectrum: ($DMSOd_6$) 2.19 (s, 3H), 3.03 (s, 9H), 7.24 (m, 2H), 7.45 (m, 5H), 7.59 (m, 1H), 7.71 (m, 1H), 7.27 (m, 1H), 7.77 (d, 1H), 7.82 (d, 1H), 9.94 (br s, 1H), 10.24 (br s, 1H); Mass Spectrum: $M-H^-$ 465.

The N-[5-(3-dimethylaminobenzamido)-2-methylphenyl]-3-aminobenzamide used as a starting material was prepared as follows :-

3-Nitrobenzoyl chloride (1.52 g) was added to a mixture of N-(3-amino-4-methylphenyl)-3-dimethylaminobenzamide (2 g), pyridine (1.2 ml) and methylene chloride (40 ml) and the resultant mixture was stirred at ambient temperature for 96 hours. The precipitate was isolated, washed in turn with methylene chloride and diethyl ether and dried

under vacuum at 60°C. There was thus obtained N-[5-(3-dimethylaminobenzamido)-2-methylphenyl]-3-nitrobenzamide (2.48 g); m.p. 219-220°C; NMR Spectrum: ($DMSOd_6$) 2.2 (s, 3H), 2.95 (s, 6H), 6.92 (d, 1H), 7.23 (m, 3H), 7.28 (t, 1H), 7.58 (m, 1H), 7.83 (m, 2H), 8.43 (m, 2H), 8.8 (d, 1H), 10.12 (br s, 1H), 10.33 (br s, 1H); Mass Spectrum: $M-H^-$ 417.

10% Palladium-on-carbon (0.3 g) was added to a solution of the material so obtained in methanol (300 ml) and the mixture was stirred under an atmosphere of hydrogen. After cessation of hydrogen uptake, the catalyst was removed by filtration and the filtrate was evaporated. The residue was dried under vacuum at 60°C. There was thus obtained the required starting material (1.81 g); NMR Spectrum: ($DMSOd_6$) 2.18 (s, 3H), 2.95 (s, 6H), 5.26 (br s, 2H), 6.73 (m, 1H), 6.89 (m, 1H), 7.15 (m, 3H), 7.21 (m, 3H), 7.27 (m, 1H), 7.57 (m, 1H), 7.77 (d, 1H), 9.63 (br s, 1H), 10.07 (br s, 1H); Mass Spectrum: $M+H^+$ 390.

Example 28

N-[5-(3-dimethylaminobenzamido)-2-methylphenyl]-3-(N-methylmethanesulphonylamino)benzamide

Methyl iodide (0.1 g) was added to a mixture of N-[5-(3-dimethylaminobenzamido)-2-methylphenyl]-3-methanesulphonylaminobenzamide (0.3 g), caesium carbonate (0.23 g) and DMF (20 ml) and the resultant mixture was stirred at ambient temperature for 18 hours. The reaction mixture was poured into water (250 ml). The precipitate was isolated, washed in turn with water and diethyl ether and dried under vacuum at 60°C. There was thus obtained the title compound (0.23 g); m.p. 168-169°C; NMR Spectrum: ($DMSOd_6$) 2.19 (s, 3H), 2.95 (s, 6H), 3.0 (s, 3H), 6.9 (d, 1H), 7.21 (m, 3H), 7.29 (t, 1H), 7.58 (m, 3H), 7.81 (d, 1H), 7.9 (d, 1H), 7.98 (d, 1H) 9.97 (br s, 1H), 10.09 (br s, 1H); Mass Spectrum: $M+H^+$ 481.

Example 29

N-[5-(3-dimethylaminobenzamido)-2-methylphenyl]-3-(2-hydroxy-3-piperidinopropoxy)benzamide

Piperidine (3 g) was added to a stirred solution of N-[5-(3-dimethylaminobenzamido)-2-methylphenyl]-3-(2,3-epoxypropoxy)benzamide (0.19 g) in a mixture of methylene chloride (3 ml) and methanol (3 ml). The resultant solution was stirred at ambient temperature for

18 hours. The mixture was evaporated and the residue was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride and methanol as eluent. There was thus obtained the title compound (0.19 g); NMR Spectrum: ($DMSOd_6$) 1.6 (m, 6H), 2.18 (s, 3H), 2.92 (m, 12H), 4.02 (m, 2H), 4.22 (m, 1H), 6.9 (m, 1H), 7.2 (m, 4H), 7.29 (t, 1H), 7.43 (t, 1H), 7.57 (m, 3H), 7.8 (d, 1H), 9.92 (br s, 1H), 10.12 (br s, 1H); Mass Spectrum: $M+H^+$ 531.

The N-[5-(3-dimethylaminobenzamido)-2-methylphenyl]-3-(2,3-epoxypropoxy)benzamide used as a starting material was prepared as follows :-

1-Bromo-2,3-epoxypropane (2.64 g) was added to a stirred mixture of N-[5-(3-dimethylaminobenzamido)-2-methylphenyl]-3-hydroxybenzamide (1.5 g), caesium carbonate (3.14 g) and DMA (100 ml) and the resultant solution was stirred at ambient temperature for 18 hours. The mixture was poured into water (750 ml). The precipitate was isolated and washed in turn with water and diethyl ether. The material so obtained was dissolved in methylene chloride, dried ($MgSO_4$) and evaporated. The solid was dried under vacuum at 60°C. There was thus obtained the required starting material (1.55 g); NMR Spectrum: ($DMSOd_6$) 2.17 (s, 3H), 2.72 (m, 1H), 2.85 (m, 1H), 2.94 (s, 6H), 3.14 (m, 2H), 3.9 (m, 1H), 4.41 (m, 1H), 6.89 (d, 1H), 7.2 (m, 4H), 7.27 (t, 1H), 7.43 (t, 1H), 7.56 (m, 3H), 7.79 (d, 1H), 9.87 (br s, 1H), 10.09 (br s, 1H); Mass Spectrum: $M-H^-$ 444.

Example 30

N-[5-(3-dimethylaminobenzamido)-2-methylphenyl]-3-(2-hydroxy-3-morpholinopropoxy)benzamide

Using an analogous procedure to that described in Example 29, morpholine was reacted with N-[5-(3-dimethylaminobenzamido)-2-methylphenyl]-3-(2,3-epoxypropoxy)-benzamide to give the title compound in 64% yield; NMR Spectrum: ($DMSOd_6$) 2.2 (s, 3H), 2.44 (m, 4H), 2.94 (s, 6H), 3.15 (m, 1H), 3.55 (t, 4H), 3.96 (m, 2H), 4.06 (m, 1H), 4.89 (m, 1H), 6.9 (m, 1H), 7.14 (m, 1H), 7.21 (m, 3H), 7.32 (t, 1H), 7.42 (t, 1H), 7.56 (m, 3H), 7.79 (d, 1H), 9.88 (br s, 1H), 10.08 (br s, 1H); Mass Spectrum: $M+H^+$ 533.

Example 31

N-[5-(3-dimethylaminobenzamido)-2-methylphenyl]-3-(2-hydroxy-3-methylaminopropoxy)benzamide

In an analogous procedure to that described in Example 29, a 33% solution of methylamine in ethanol was added to a solution of N-[5-(3-dimethylaminobenzamido)-2-methylphenyl]-3-(2,3-epoxypropoxy)benzamide in a 1:1 mixture of methylene chloride and methanol and the resultant solution was stirred at ambient temperature for 18 hours. The mixture was evaporated and the residue was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride and methanol as eluent. There was thus obtained the title compound in 59% yield; NMR Spectrum: ($DMSOd_6$) 2.18 (s, 3H), 2.56 (s, 3H), 2.94 (s, 6H), 3.11 (m, 2H), 4.05 (m, 2H), 4.75 (m, 1H), 6.9 (m, 1H), 7.2 (m, 4H), 7.29 (t, 1H), 7.45 (t, 1H), 7.57 (m, 3H), 7.8 (d, 1H), 9.09 (br s, 1H), 10.11 (br s, 1H); Mass Spectrum: $M+H^+$ 477.

Example 32

N-[5-(3-dimethylaminobenzamido)-2-methylphenyl]-3-(2-hydroxy-3-dimethylaminopropoxy)benzamide

Using an analogous procedure to that described in Example 31, N-[5-(3-dimethylaminobenzamido)-2-methylphenyl]-3-(2,3-epoxypropoxy)benzamide was reacted with dimethylamine to give the title compound in 68% yield; NMR Spectrum: ($DMSOd_6$) 2.18 (s, 3H), 2.56 (s, 6H), 2.95 (s, 6H), 2.78 (m, 2H), 4.03 (m, 2H), 4.18 (m, 1H), 6.9 (m, 1H), 7.16 (m, 1H), 7.23 (m, 3H), 7.3 (t, 1H), 7.43 (t, 1H), 7.57 (m, 3H), 7.8 (d, 1H), 9.93 (br s, 1H), 10.11 (br s, 1H); Mass Spectrum: $M+H^+$ 491.

Example 33

N-[5-(3-dimethylaminobenzamido)-2-methylphenyl]-3-carboxymethoxybenzamide

Trifluoroacetic acid (10 ml) was added to a stirred solution of N-[5-(3-dimethylaminobenzamido)-2-methylphenyl]-3-tert-butoxycarbonylmethoxybenzamide (0.5 g) in methylene chloride (10 ml) and the mixture was stirred at ambient temperature for 1 hour. The mixture was evaporated and the residue was azeotroped with toluene. The resultant gum was triturated under diethyl ether. The solid so obtained was

isolated and dried under vacuum at 60°C. There was thus obtained the title compound as its trifluoroacetic acid salt (0.39 g); NMR Spectrum: ($DMSOd_6$) 2.17 (s, 3H), 2.93 (s, 6H), 4.76 (s, 2H), 6.93 (m, 1H), 7.13 (m, 1H), 7.23 (m, 3H), 7.3 (t, 1H), 7.43 (t, 1H), 7.51 (d, 1H), 7.59 (d, 2H), 7.78 (d, 1H), 9.88 (br s, 1H), 10.1 (br s, 1H); Mass Spectrum: $M-H^-$ 446.

The N-[5-(3-dimethylaminobenzamido)-2-methylphenyl]-3-tert-butoxycarbonylmethoxybenzamide was prepared as follows :-

tert-Butyl bromoacetate (0.24 g) was added to a stirred mixture of N-[5-(3-dimethylaminobenzamido)-2-methylphenyl]-3-hydroxybenzamide (0.45 g), potassium carbonate (0.64 g) and DMA (8 ml) and the resultant solution was stirred and heated to 60°C for 18 hours. The reaction mixture was allowed to cool to ambient temperature and poured into water (150 ml). The resultant precipitate was isolated, washed in turn with water (50 ml) and diethyl ether (50 ml) and dried under vacuum at 60°C. There was thus obtained the required starting material (0.516 g); NMR Spectrum: ($DMSOd_6$) 1.42 (s, 9H), 2.18 (s, 3H), 2.94 (s, 6H), 4.73 (s, 2H), 6.89 (d, 1H), 7.11 (d, 1H), 7.21 (m, 2H), 7.28 (t, 1H), 7.43 (t, 1H), 7.48 (s, 1H), 7.59 (d, 2H), 7.78 (s, 1H), 9.86 (s, 1H), 10.09 (s, 1H); Mass Spectrum: $M+H^+$ 504.

Example 34

N-[5-(3-dimethylaminobenzamido)-2-methylphenyl]-4-(3-morpholinopropylamino)benzamide

Using an analogous procedure to that described in Example 20, N-[5-(3-dimethylaminobenzamido)-2-methylphenyl]-4-fluorobenzamide was reacted with 3-morpholinopropylamine to give the title compound in 3% yield; NMR Spectrum: ($DMSOd_6$) 1.77 (m, 2H), 2.24 (s, 3H), 2.46 (m, 6H), 3.02 (s, 6H), 3.16 (q, 2H), 3.65 (t, 4H), 6.33 (t, 1H), 6.67 (d, 2H), 6.97 (m, 1H), 7.28 (m, 2H), 7.36 (t, 1H), 7.62 (m, 1H), 7.83 (m, 3H), 9.45 (s, 1H), 10.06 (s, 1H); Mass Spectrum: $M+H^+$ 516.

The N-[5-(3-dimethylaminobenzamido)-2-methylphenyl]-4-fluorobenzamide used as a starting material was prepared as follows :-

Oxalyl chloride (13.0 ml) was added dropwise to a stirred mixture of 3-dimethylaminobenzoic acid (20.3 g) and DMF (a few drops) which had been cooled to 0°C. The mixture was allowed to warm to ambient temperature and was stirred for 4 hours. The

resultant mixture was evaporated and the residue was dissolved in methylene chloride (150 ml). 4-Methyl-3-nitroaniline (15.2 g) and triethylamine (27.9 ml) were added in turn and the resultant mixture was stirred at ambient temperature for 16 hours. The reaction mixture was washed in turn with water, with a saturated solution of sodium bicarbonate and with brine, dried ($MgSO_4$) and evaporated. The residue was triturated under a mixture of ethyl acetate and isohexane. The solid so obtained was filtered off and recrystallised from ethanol to give N-(3-nitro-4-methylphenyl)-3-dimethylaminobenzamide (6.1 g); NMR Spectrum: ($DMSOd_6$) 2.46 (s, 3H), 2.95 (s, 6H), 6.92 (d, 1H), 7.22 (m, 2H), 7.32 (t, 1H), 7.45 (d, 1H), 7.97 (d, 1H), 8.53 (s, 1H), 10.43 (s, 1H); Mass Spectrum: $M+H^+$ 300;

After repetition of the previous reactions, a sample of the product (8.25 g) was added to a stirred suspension of ammonium formate (17.4 g), and 10% palladium-on-carbon (1 g) in methanol (250 ml). The mixture was stirred and heated to reflux for 4 hours. The mixture was allowed to cool and then filtered. The filtrate was evaporated and water was added to the residue. The resultant solid was isolated and washed in turn with water, with ethyl acetate and with diethyl ether. The solid was dried in a vacuum oven at 40°C to give N-(3-amino-4-methylphenyl)-3-dimethylaminobenzamide (6.89 g); NMR Spectrum: ($DMSOd_6$) 2.0 (s, 3H), 2.94 (s, 6H), 4.78 (s, 2H), 6.82 (m, 3H), 7.07 (s, 1H), 7.17 (m, 2H), 7.25 (m, 1H), 9.74 (s, 1H); Mass Spectrum: $M+H^+$ 270.

4-Fluorobenzoyl chloride (1.3 g) was added to a mixture of N-(3-amino-4-methylphenyl)-3-dimethylaminobenzamide (2 g), pyridine (0.88 g) and methylene chloride (15 ml) and the resultant mixture was stirred at ambient temperature for 18 hours. The mixture was washed with water and with a saturated aqueous sodium bicarbonate solution and dried ($MgSO_4$). The solid so obtained was washed with diethyl ether and dried under vacuum at 60°C. There was thus obtained the required starting material (1.39 g). NMR Spectrum : ($DMSOd_6$) 2.18 (s, 3H), 2.95 (s, 6H), 6.9 (m, 1H), 7.21 (m, 3H), 7.26 (d, 1H), 7.35 (t, 2H), 7.58 (m, 1H), 7.8 (d, 1H), 8.05 (m, 2H), 9.9 (br s, 1H), 10.08 (br s, 1H); Mass Spectrum: $M+H^+$ 392.

Example 35

N-[5-(3-dimethylaminobenzamido)-2-methylphenyl]-2-(3-morpholinopropylamino)benzamide

Using an analogous procedure to that described in Example 20, N-[5-(3-dimethylaminobenzamido)-2-methylphenyl]-2-fluorobenzamide was reacted with 3-morpholinopropylamine to give the title compound in 33% yield; m.p. 239-240°C; NMR Spectrum: ($DMSOd_6$) 1.7 (m, 2H), 2.17 (s, 3H), 2.31 (m, 6H), 2.95 (s, 6H), 3.15 (q, 2H), 3.53 (t, 4H), 6.6 (t, 1H), 6.72 (d, 1H), 6.89 (m, 1H), 7.2 (m, 3H), 7.3 (m, 2H), 7.54 (m, 1H), 7.65 (m, 1H), 7.75 (m, 2H), 9.69 (s, 1H), 10.06 (s, 1H); Mass Spectrum: $M+H^+$ 516.

The N-[5-(3-dimethylaminobenzamido)-2-methylphenyl]-2-fluorobenzamide used as a starting material was prepared by the reaction of N-(3-amino-4-methylphenyl)-3-dimethylaminobenzamide and 2-fluorobenzoyl chloride using an analogous procedure to that described in Example 10. The product gave the following data : NMR Spectrum: ($DMSOd_6$) 2.22 (s, 3H), 2.95 (s, 6H), 6.9 (d, 1H), 7.26 (m, 6H), 7.56 (m, 2H), 7.71 (t, 1H), 7.92 (s, 1H), 9.82 (s, 1H), 10.1 (s, 1H); Mass Spectrum: $M+H^+$ 392.

Example 36

N-[5-(3-dimethylaminobenzamido)-2-methylphenyl]-4-(3-dimethylamino-N-methylpropylamino)benzamide

Using an analogous procedure to that described in Example 20, N-[5-(3-dimethylaminobenzamido)-2-methylphenyl]-2-fluorobenzamide was reacted with N,N,N'-trimethyl-1,3-propanediamine to give the title compound in 29% yield; m.p. 178-179°C; NMR Spectrum: ($DMSOd_6$) 1.64 (m, 2H), 2.13 (s, 6H), 2.17 (s, 3H), 2.22 (t, 2H), 2.95 (m, 9H), 3.41 (t, 2H), 6.73 (d, 2H), 6.89 (m, 1H), 7.19 (m, 3H), 7.29 (t, 1H), 7.56 (m, 1H), 7.8 (d, 1H), 7.84 (d, 2H), 9.44 (s, 1H), 10.05 (s, 1H); Mass Spectrum: $M+H^+$ 488.

Example 37

N-(5-benzamido-2-methylphenyl)-3-(chloromethyl)benzamide

Triethylamine (2.0 ml) was added to a stirred mixture of N-(3-amino-4-methylphenyl)benzamide (3.0 g), 3-chloromethylbenzoyl chloride (2.76 g), 4-dimethylaminopyridine (0.162 g) and methylene chloride (50 ml) and the reaction mixture

was stirred at ambient temperature for 16 hours. The mixture was evaporated and the residue was triturated under 2N aqueous hydrochloric acid solution. The solid so obtained was isolated, washed in turn with a saturated aqueous sodium bicarbonate solution, water and isohexane and dried under vacuum at 55°C. There was thus obtained the title compound (5.1 g); NMR Spectrum: ($DMSOd_6$) 2.19 (s, 3H), 4.85 (s, 2H), 7.23 (d, 1H), 7.55 (m, 5H), 7.66 (d, 1H), 7.84 (s, 1H), 7.95 (m, 3H), 8.05 (s, 1H), 9.96 (s, 1H), 10.22 (s, 1H); Mass Spectrum: $M-H^-$ 377.

The N-(3-amino-4-methylphenyl)benzamide used as a starting material was prepared as follows :-

Benzoyl chloride (1.9 ml) was added to a stirred mixture of 2,4-diaminotoluene (2 g), triethylamine (5.57 ml) and methylene chloride (80 ml) and the mixture was stirred at ambient temperature for 16 hours. The mixture was washed with a saturated aqueous solution of sodium bicarbonate. The organic phase was dried ($MgSO_4$) and evaporated. The residue was triturated with a mixture of ethyl acetate and diethyl ether. There was thus obtained the required starting material (1.32 g); NMR Spectrum: ($DMSOd_6$) 2.01 (s, 3H), 4.8 (s, 2H), 6.82 (m 2H), 7.11 (s, 1H), 7.5 (m, 3H), 7.91 (m, 2H), 9.86 (s, 1H); Mass Spectrum: $M+H^+$ 227.

Example 38

N-(5-benzamido-2-methylphenyl)-4-(chloromethyl)benzamide

Using an analogous procedure to that described in Example 37, 4-chloromethylbenzoyl chloride was reacted with N-(3-amino-4-methylphenyl)benzamide to give the title compound in 99% yield; NMR Spectrum: ($DMSOd_6$) 2.19 (s, 3H), 4.84 (s, 2H), 7.22 (d, 1H), 7.54 (m, 6H), 7.84 (s, 1H), 7.96 (m, 4H), 9.92 (s, 1H), 10.22 (s, 1H); Mass Spectrum: $M-H^-$ 377.

Example 39

N-[5-(3-trifluoromethylbenzamido)-2-methylphenyl]-3-(chloromethyl)benzamide

Using an analogous procedure to that described in Example 37, 3-chloromethylbenzoyl chloride was reacted with N-(3-amino-4-methylphenyl)-

3-trifluoromethylbenzamide to give the title compound in 94% yield; NMR Spectrum: ($DMSOd_6$) 2.2 (s, 3H), 4.85 (s, 2H), 7.25 (d, 1H), 7.6 (m, 3H), 7.8 (m, 2H), 7.95 (d, 2H), 8.05 (s, 1H), 8.16 (m, 2H), 9.96 (s, 1H), 10.44 (s, 1H); Mass Spectrum: $M-H^-$ 445.

The N-(3-amino-4-methylphenyl)-3-trifluoromethylbenzamide used as a starting material was prepared as follows :-

A mixture of 3-trifluoromethylbenzoyl chloride (9.9 ml), 3-nitro-4-methylaniline (10 g) and pyridine (100 ml) was stirred and heated to 80°C for 2 hours. The reaction mixture was evaporated and the residue was triturated under 2N aqueous hydrochloric acid solution. The solid so obtained was isolated, washed in turn with a saturated aqueous sodium bicarbonate solution, water and isohexane and dried under vacuum at 55°C to give N-(4-methyl-3-nitrophenyl)-3-trifluoromethylbenzamide as a solid (21.9 g); NMR Spectrum: ($DMSOd_6$) 7.49 (d, 1H), 7.78 (m, 1H), 7.99 (m, 2H), 8.27 (m, 2H), 8.51 (s, 1H), 10.77 (s, 1H); Mass Spectrum: $M-H^-$ 323.

10% Palladium-on-charcoal (1.0 g) was added to a solution of a portion (10 g) of the material so obtained in methanol (250 ml). Ammonium formate (19.0 g) was added and the resultant mixture was stirred and heated to reflux for 1 hour. The mixture was filtered through diatomaceous earth and the filtrate was evaporated. The residue was triturated under water. The resultant solid was isolated and dried under vacuum at 55°C to give N-(3-amino-4-methylphenyl)-3-trifluoromethylbenzamide as a solid (7.98 g); NMR Spectrum: ($DMSOd_6$) 2.01 (s, 3H), 4.83 (s, 2H), 6.85 (m, 2H), 7.08 (s, 1H), 7.74 (t, 1H), 7.92 (d, 1H), 8.2 (d, 1H), 10.11 (s, 1H); Mass Spectrum: $M-H^-$ 293.

Example 40

N-[5-(3-trifluoromethylbenzamido)-2-methylphenyl]-4-(chloromethyl)benzamide

Using an analogous procedure to that described in Example 37, 4-chloromethylbenzoyl chloride was reacted with N-(3-amino-4-methylphenyl)-3-trifluoromethylbenzamide to give the title compound in 94% yield; NMR Spectrum: ($DMSOd_6$) 2.21 (s, 3H), 4.84 (s, 2H), 7.25 (d, 1H), 7.57 (m, 3H), 7.76 (t, 1H), 7.83 (d, 1H), 7.96 (m, 3H), 8.26 (m, 2H), 9.92 (s, 1H), 10.44 (s, 1H); Mass Spectrum: $M-H^-$ 445.

Example 41

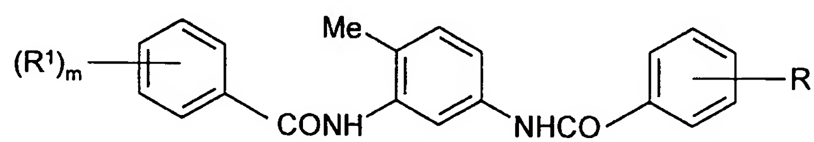
N-[5-(4-cyanobenzamido)-2-methylphenyl]-3-(diethylaminomethyl)benzamide

Diethylamine hydrochloride (0.33 g) was added to a stirred mixture of N-[5-(4-cyanobenzamido)-2-methylphenyl]-3-chloromethylbenzamide (0.4 g), potassium carbonate (0.5 g) and acetone (6 ml) and the reaction mixture was stirred and heated to 55°C for 16 hours. The reaction mixture was evaporated and the residue was triturated under water. The solid was isolated and dried under vacuum at 55°C to give the title compound (0.24 g); NMR Spectrum: ($DMSOd_6$) 0.95 (t, 6H), 2.19 (s, 3H), 3.58 (s, 2H), 7.22 (d, 1H), 7.5 (m, 3H), 7.85 (m, 3H), 7.99 (d, 2H), 8.12 (d, 2H); Mass Spectrum: $M-H^-$ 439.

Example 42

Using an analogous procedure to that described in Example 41, the appropriate amine was reacted with the appropriate chloromethylbenzamide to give the compounds described in Table IV.

Table IV



No.	$(R^1)_m$	R	Note
1	4-(3-methoxypropylaminomethyl)	3-trifluoromethyl	a
2	4-(N-methyl-N-propylaminomethyl)	4-cyano	b
3	4-(diethylaminomethyl)	3-dimethylamino	c
4	3-[N-(3-dimethylaminopropyl)-N-methylaminomethyl]	3-trifluoromethyl	d
5	4-(2-morpholinoethylaminomethyl)	hydrogen	e
6	4-(N-benzyl-N-methylaminomethyl)	hydrogen	f

Notes

a) The amine reactant was 3-methoxypropylamine. The product gave the following data : NMR ($DMSOd_6$) 1.72 (m, 2H), 2.2 (s, 3H), 3.2 (m, 7H), 3.63 (s, 2H), 7.24 (d, 1H), 7.48 (m, 2H), 7.6 (d, 1H), 7.79 (m, 2H), 7.95 (m, 3H), 8.27 (m, 2H), 9.85 (s, 1H), 10.47 (s, 1H); Mass M-H 498.

b) The amine reactant was N-methyl-N-propylamine. The product gave the following data : NMR ($DMSOd_6$) 0.94 (t, 3H), 1.46 (m, 2H), 2.11 (s, 3H), 2.2 (s, 3H), 2.3 (t, 2H), 3.51 (s, 2H), 7.22 (d, 1H), 7.42 (d, 2H), 7.57 (d, 1H), 7.82 (d, 1H), 7.93 (d, 2H), 7.98 (d, 2H), 8.12 (d, 2H); Mass M-H 439.

c) The product gave the following data : NMR ($DMSOd_6$) 0.98 (t, 6H), 2.19 (s, 3H), 2.95 (s, 6H), 3.59 (s, 2H), 6.9 (d, 1H), 7.2 (m, 3H), 7.29 (d, 1H), 7.45 (d, 2H), 7.58 (d, 1H), 7.80 (s, 1H), 7.93 (d, 2H), 9.81 (s, 1H), 10.08 (s, 1H); Mass M+H 460.

d) The amine reactant was N-(3-dimethylaminopropyl)-N-methylamine. The product gave the following data : NMR ($DMSOd_6$) 1.58 (m, 2H), 2.09 (s, 6H), 2.13 (s, 3H), 2.21 (m, 5H), 2.36 (t, 2H), 3.52 (s, 2H), 7.23 (d, 1H), 7.4-8.0 (m, 8H), 8.27 (m, 2H); Mass M-H 525.

e) The amine reactant was 2-morpholinoethylamine. The product gave the following data : NMR ($DMSOd_6$) 2.19 (s, 3H), 2.2-2.6 (m, 8H), 3.55 (m, 4H), 3.73 (d, 2H), 7.21 (d, 1H), 7.4-7.6 (m, 6H), 7.83 (s, 1H), 7.94 (m, 4H), 9.84 (s, 1H), 10.22 (s, 1H); Mass M-H 471.

f) The amine reactant was N-benzyl-N-methylamine. The product gave the following data : NMR ($DMSOd_6$) 2.1 (s, 3H), 2.19 (s, 3H), 3.52 (s, 2H), 3.58 (s, 2H), 7.2-7.6 (m, 12H), 7.82 (s, 1H), 7.95 (m, 4H), 9.85 (broad s, 1H), 10.22 (broad s, 1H); Mass M-H 462.

Example 43

N-[5-(3-cyclohexylpropionamido)-2-methylphenyl]-4-(diethylaminomethyl)benzamide

Using an analogous procedure to that described in Example 22 except that the step of washing the reaction mixture with a 1M aqueous citric acid solution was omitted, N-(5-amino-2-methylphenyl)-4-diethylaminomethylbenzamide was reacted with 3-cyclohexylpropionyl chloride (obtained by the reaction of 3-cyclohexylpropionic acid and

oxalyl chloride using a conventional procedure) to give the title compound; Mass Spectrum: $M+H^+$ 450.

Example 44

N-[5-(4-cyclohexylbutyramido)-2-methylphenyl]-4-(diethylaminomethyl)benzamide

Using an analogous procedure to that described in Example 22 except that the step of washing the reaction mixture with a 1M aqueous citric acid solution was omitted, N-(5-amino-2-methylphenyl)-4-diethylaminomethylbenzamide was reacted with 4-cyclohexylbutyryl chloride (obtained by the reaction of 4-cyclohexylbutyric acid and oxalyl chloride using a conventional procedure) to give the title compound; Mass Spectrum: $M+H^+$ 464.

Example 45

N-[2-methyl-5-(3-morpholinobenzamido)phenyl]-3-(2,3-epoxypropoxy)benzamide

1-Bromo-2,3-epoxypropane (1.5 ml) was added to a stirred mixture of N-[2-methyl-5-(3-morpholinobenzamido)phenyl]-3-hydroxybenzamide (1.5 g), caesium carbonate (2.84 g) and DMA (100 ml) and the resultant solution was stirred at ambient temperature for 18 hours. The mixture was poured into water (750 ml). The precipitate was isolated, washed with water and dried under vacuum at 60°C. There was thus obtained the title compound (1.3 g); NMR Spectrum: ($DMSOd_6$) 2.19 (s, 3H), 2.73 (m, 1H), 2.85 (m, 1H), 3.2 (t, 4H), 3.75 (t, 4H), 3.91 (m, 1H), 4.43 (m, 1H), 7.2 (m, 3H), 7.37 (m, 4H), 7.66 (m, 3H), 7.56 (m, 3H), 7.8 (s, 1H), 9.9 (s, 1H), 10.14 (s, 1H); Mass Spectrum: $M-H^-$ 486.

Example 46

N-[5-(3-dimethylaminobenzamido)-2-methylphenyl]-3-{3-[N-(3-dimethylaminopropyl)-N-methylamino]-2-hydroxypropoxy}benzamide

Using an analogous procedure to that described in Example 31, N-[5-(3-dimethylaminobenzamido)-2-methylphenyl]-3-(2,3-epoxypropoxy)benzamide was reacted with N-(3-dimethylaminopropyl)-N-methylamine to give the title compound in 45% yield; NMR Spectrum: ($DMSOd_6$) 1.8 (m, 2H), 2.18 (s, 3H), 2.33 (s, 3H), 2.58 (s, 6H), 2.6 (m, 2H), 2.92 (t, 2H), 2.96 (s, 6H), 4.03 (m, 5H), 6.9 (m, 1H), 7.15 (m, 1H), 7.2 (m, 3H), 7.28

(t, 1H), 7.48 (t, 1H), 7.56 (m, 2H), 7.8 (d, 1H), 9.95 (s, 1H), 10.13 (s, 1H); Mass Spectrum: $M+H^+$ 562.

Example 47

N-[2-methyl-5-(3-morpholinobenzamido)phenyl]-4-(6-chloropyrimidin-4-yloxy)benzamide

4,6-Dichloropyrimidine (0.103 g) was added to a stirred mixture of N-[2-methyl-5-(3-morpholinobenzamido)phenyl]-4-hydroxybenzamide (0.3 g), caesium carbonate (0.453 g) and DMA (7.5 ml) and the resultant solution was stirred at ambient temperature for 18 hours. The mixture was poured into water (200 ml) and extracted with ethyl acetate. The organic phase was washed with water, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride and methanol as eluent. The material so obtained was triturated under diethyl ether. The resultant solid was isolated, washed with diethyl ether and dried under vacuum at 60°C. There was thus obtained the title compound (0.2 g); NMR Spectrum: ($DMSOd_6$) 2.19 (s, 3H), 3.2 (t, 4H), 3.74 (t, 4H), 7.12 (m, 1H), 7.23 (m, 1H), 7.41 (m, 6H), 7.58 (m, 1H), 7.82 (d , 3H); 8.06 (d, 2H), 8.67 (s , 1H), 9.93 (s, 1H), 10.12 (s , 1H); Mass Spectrum: $M+H^+$ 544.

Example 48

N-[2-methyl-5-(3-morpholinobenzamido)phenyl]-3-(6-chloropyrimidin-4-yloxy)benzamide

Using an analogous procedure to that described in Example 47, 4,6-dichloropyrimidine was reacted with N-[2-methyl-5-(3-morpholinobenzamido)phenyl]-3-hydroxybenzamide to give the title compound in 42% yield; NMR Spectrum: ($DMSOd_6$) 2.18 (s, 3H), 3.14 (t, 4H), 3.73 (t, 4H), 7.22 (d, 1H), 7.34 (m, 2H), 7.47 (m, 3H), 7.57 (m, 1H), 7.63 (t, H), 7.81 (d, 1H), 7.93 (d, 1H), 8.66 (s, 1H), 9.96 (s, 1H), 10.14 (s , 1H); Mass Spectrum: $M+H^+$ 544.

Example 49

N-[2-methyl-5-(3-morpholinobenzamido)phenyl]-4-methoxy-3-piperidin-4-yloxybenzamide

Using an analogous procedure to that described in Example 25, 3-(1-tert-butoxycarbonylpiperidin-4-yloxy)-4-methoxybenzoic acid was reacted with N-(3-amino-4-methylphenyl)-3-morpholinobenzamide to give N-[2-methyl-5-(3-morpholinobenzamido)phenyl]-3-(1-tert-butoxycarbonylpiperidin-4-yloxy)-4-methoxybenzamide in 48% yield and that product was treated with trifluoroacetic acid. The reaction mixture was evaporated, water (40 ml) was added to the residue and the mixture was basified by the addition of 1N aqueous sodium hydroxide solution. The water was decanted and the residue was titurated under diethyl ether. The resultant solid was isolated, dissolved in water (30 ml) and basified by the addition of potassium carbonate. The precipitate was isolated and dried. There was thus obtained the title compound in 26% yield; NMR Spectrum: ($DMSOd_6$) 1.48 (m, 2H), 1.9 (m, 2H), 2.18 (s, 3H), 3.19 (m, 4H), 3.75 (m, 4H), 3.83 (s, 3H), 4.39 (m, 1H), 7.1 (m, 2H), 7.21 (d, 1H), 7.4 (m, 3H), 7.6 (m, 3H), 7.79 (s, 1H), 9.72 (s, 1H), 10.1 (s, 1H); Mass Spectrum: $M+H^+$ 545.

The 3-(1-tert-butoxycarbonylpiperidin-4-yloxy)-4-methoxybenzoic acid used as a starting material was obtained by the reaction of N-tert-butoxycarbonyl-4-hydroxypiperidine and ethyl 3-hydroxy-4-methoxybenzoate (J. Amer. Chem. Soc., 1953, 75, 2630-2631) using an analogous procedure to that described in the portion of Example 25 which is concerned with the preparation of starting materials. There was thus obtained the required starting material as a solid; NMR Spectrum: ($DMSOd_6$) 1.2 (s, 9H), 1.5 (m, 2H), 1.85 (m, 2H), 3.18 (m, 2H), 3.64 (m, 2H), 3.81 (s, 3H), 4.48 (m, 1H), 7.05 (d, 1H), 7.48 (m, 1H), 7.58 (m, 1H); Mass Spectrum: $M-H^-$ 350.

Example 50

N-[5-(3-fluoro-5-morpholinobenzamido)-2-methylphenyl]-3-piperidin-4-yloxybenzamide

1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.23 g) was added to a stirred mixture of 3-(1-tert-butoxycarbonylpiperidin-4-yloxy)benzoic acid (0.321 g), N-(3-amino-4-methylphenyl)-3-fluoro-5-morpholinobenzamide (0.329 g), 1-hydroxybenzotriazole (0.202 g) and DMF (5 ml) which had been cooled to 0°C. The

reaction mixture was allowed to warm to ambient temperature and was stirred for 40 hours. The reaction mixture was partitioned between ethyl acetate and water. The organic phase was washed with water, and with a saturated aqueous sodium bicarbonate solution, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride and methanol as eluent. There was thus obtained N-[5-(3-fluoro-5-morpholinobenzamido)-2-methylphenyl]-3-(1-tert-butoxycarbonylpiperidin-4-yloxy)benzamide (0.423 g); NMR Spectrum: ($DMSOd_6$) 1.38 (s, 9H), 1.57 (m, 2H), 1.93 (m, 2H), 2.18 (s, 3H), 3.16 (m, 2H), 3.2 (t, 4H), 3.65 (m, 2H), 3.74 (t, 4H), 4.65 (m, 1H), 6.95 (m, 1H), 7.12 (m, 1H), 7.2 (m, 2H), 7.28 (d, 1H), 7.41 (t, 1H), 7.57 (m, 3H), 7.78 (d, 1H), 9.82 (s, 1H), 10.15 (s, 1H); Mass Spectrum: $M+H^+$ 633.

Trifluoroacetic acid (0.9 ml) was added to a stirred solution of the material so obtained in methylene chloride (9 ml) which had been cooled to 0°C. The reaction mixture was stirred for 3 hours and allowed to warm to ambient temperature. The mixture was evaporated and the residue was triturated under diethyl ether to give the title compound, as its trifluoroacetate salt. The solid so obtained was dissolved in water (20 ml) and basified by the addition of potassium carbonate. The resultant precipitate was collected and dried under vacuum to give the title compound (0.214 g); NMR Spectrum: ($DMSOd_6$) 1.6 (m, 2H), 1.97 (m, 2H), 2.18 (s, 3H), 2.77 (m, 2H), 3.03 (m, 2H), 3.2 (t, 4H), 3.76 (t, 4H), 4.56 (m, 1H), 6.96 (d, 1H), 7.1 (d, 1H), 7.18 (d, 1H), 7.21 (d, 1H), 7.27 (s, 1H), 7.4 (t, 1H), 7.57 (m, 3H), 7.78 (s, 1H), 9.83 (s, 1H), 10.15 (s, 1H); Mass Spectrum: $M+H^+$ 533.

The N-(3-amino-4-methylphenyl)-3-fluoro-5-morpholinobenzamide used as a starting material was obtained as follows :-

A solution of 3,5-difluorobenzoyl chloride (2.82 g) in methylene chloride (20 ml) was added to a stirred mixture of 4-methyl-3-nitroaniline (2.28 g), triethylamine (4.35 ml) and methylene chloride (80 ml). The resultant mixture was stirred at ambient temperature for 16 hours. The precipitate was isolated, washed with methylene chloride and dried. There was thus obtained N-(4-methyl-3-nitrophenyl)-3,5-difluorobenzamide; NMR Spectrum: ($DMSOd_6$) 2.43 (s, 3H), 7.43 (m, 2H), 7.63 (m, 2H), 7.95 (m, 2H), 8.43 (d, 1H), 10.42 (s, 1H); Mass Spectrum: $M+H^+$ 293.

A mixture of a portion (1 g) of the material so obtained and morpholine (5 ml) was stirred and heated to 100°C for 48 hours and then to 120°C for 24 hours. The reaction

mixture was cooled and poured into water (100 ml). The resultant solid was isolated, washed with water and dried. The material so obtained was purified by column chromatography on silica using a 1:1 mixture of isohexane and ethyl acetate as eluent. There was thus obtained N-(4-methyl-3-nitrophenyl)-3-fluoro-5-morpholinobenzamide as a solid (0.53 g); NMR Spectrum: ($DMSOd_6$) 2.46 (s, 3H), 3.22 (t, 4H), 3.75 (t, 4H), 6.98 (m, 1H), 7.12 (d, 1H), 7.27 (s, 1H), 7.46 (d, 1H), 7.96 (m, 1H), 8.43 (d, 1H), 10.48 (s, 1H); Mass Spectrum: $M+H^+$ 360.

A portion (0.483 g) of the compound so obtained was dissolved in ethyl acetate (40 ml) and hydrogenated over 10% palladium-on-carbon catalyst (0.6 g) under an atmosphere of hydrogen until the uptake of hydrogen ceased. The catalyst was removed by filtration and the filtrate was evaporated. The residue was triturated under diethyl ether (25 ml). The resultant solid was collected, washed with diethyl ether and dried. There was thus obtained the required starting material (0.341 g); NMR Spectrum: ($DMSOd_6$) 1.99 (s, 3H), 3.19 (t, 4H), 3.76 (t, 4H), 4.8 (s, 2H), 6.75 (d, 1H), 6.82 (d, 1H), 6.9 (d, 1H), 7.02 (s, 1H), 7.04 (d, 1H), 7.23 (s, 1H), 9.81 (s, 1H).

Example 51

N-[2-methyl-5-(3-piperidinobenzamido)phenyl]-3-piperidin-4-yloxybenzamide

Using an analogous procedure to that described in the first paragraph of Example 25, 3-(1-tert-butoxycarbonylpiperidin-4-yloxy)benzoic acid was reacted with N-(3-amino-4-methylphenyl)-3-piperidinobenzamide to give N-[2-methyl-5-(3-piperidinobenzamido)phenyl]-3-(1-tert-butoxycarbonylpiperidin-4-yloxy)benzamide in 57% yield; NMR Spectrum: ($DMSOd_6$) 1.39 (s, 9H), 1.54 (m, 4H), 1.62 (m, 4H), 1.91 (m, 2H), 2.19 (s, 3H), 3.2 (m, 4H), 3.65 (m, 2H), 4.64 (m, 4H), 7.09 (m, 1H), 7.19 (m, 2H), 7.27 (m, 2H), 7.41 (t, 2H), 7.58 (m, 2H), 7.79 (m, 1H), 9.83 (s, 1H), 10.09 (s, 1H); Mass Spectrum: $M-C_3H_7^+$ 557.

The product so obtained was treated with trifluoroacetic acid using an analogous procedure to that described in the second paragraph of Example 25. The reaction mixture was evaporated and the residue was triturated under diethyl ether. The solid so obtained was dissolved in water (60 ml) and the solution was basified by the addition of 1N aqueous sodium hydroxide solution. The resultant solid was isolated and dried. There was thus obtained the title compound in 66% yield; NMR Spectrum: ($DMSOd_6$) 1.5 (m, 8H), 1.91 (m,

2H), 2.18 (s, 3H), 2.57 (m, 2H), 2.93 (m, 2H), 3.2 (m, 2H), 4.45 (s, 1H), 7.1 (m, 2H), 7.2 (d, 1H), 7.28 (d, 2H), 7.4 (m, 2H), 7.56 (m, 3H), 7.78 (s, 1H), 9.83 (s, 1H), 10.09 (s, 1H); Mass Spectrum: $M+H^+$ 513.

The N-(3-amino-4-methylphenyl)-3-piperidinobenzamide used as a starting material was obtained as follows :-

A mixture of piperidine (20.9 ml), 3-fluorobenzonitrile (4.36 g) and DMSO (30 ml) was stirred and heated to 100°C for 64 hours. The mixture was allowed to cool to ambient temperature and was partitioned between diethyl ether and water. The organic phase was washed with a saturated aqueous sodium chloride solution, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography on silica using a 9:1 mixture of isohexane and ethyl acetate as eluent.. There was thus obtained 3-piperidinobenzonitrile as an oil (5.7 g); NMR Spectrum: ($CDCl_3$) 1.52 (m, 2H), 1.6 (m, 4H), 3.17 (t, 4H), 6.95 (d, 1H), 7.02 (m, 2H), 7.21 (m, 1H).

A mixture of the material so obtained, 5N aqueous sodium hydroxide solution (30 ml) and n-butanol (25 ml) was stirred and heated to reflux for 24 hours. The mixture was evaporated and the residual solid was triturated under a mixture of diethyl ether (100 ml) and water (50 ml). The aqueous layer was separated, acidified to pH5 by the addition of 1N aqueous hydrochloric acid and extracted with methylene chloride (2x50 ml). The combined organic extracts were dried ($MgSO_4$) and evaporated. There was thus obtained 3-piperidinobenzoic acid (3.1 g); NMR Spectrum: ($DMSOd_6$) 1.57 (m, 6H), 3.18 (t, 4H), 7.17 (m, 1H), 7.27 (m, 2H), 7.41 (d, 1H), 12.72 (s, 1H).

A mixture of the material so obtained, oxalyl chloride (0.93 ml), DMF (3 drops) and methylene chloride (80 ml) was stirred at ambient temperature for 4 hours. The resultant mixture was evaporated. The material so obtained was dissolved in methylene chloride (80 ml) and added to a stirred mixture of 4-methyl-3-nitroaniline (1.14 g), triethylamine (2.19 ml) and methylene chloride (80 ml). The mixture was stirred at ambient temperature for 18 hours. The mixture was then washed in turn with water, with a saturated aqueous sodium bicarbonate solution and with water, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography on silica using a 9:1 mixture of isohexane and ethyl acetate as eluent. There was thus obtained N-(4-methyl-3-nitrophenyl)-3-piperidinobenzamide as a solid (0.82 g); NMR Spectrum: ($DMSOd_6$) 1.5 (m, 2H), 1.61 (m, 4H), 2.5 (s, 3H), 3.2 (t, 4H),

7.1 (m, 1H), 7.28 (m, 2H), 7.42 (m, 1H), 7.46 (s, 1H), 8.52 (d, 1H).

A mixture of the material so obtained, 10% palladium-on-carbon catalyst (0.15 g) and methanol (150 ml) was stirred under an atmosphere pressure of hydrogen at ambient temperature for 18 hours. The catalyst was filtered off and the filtrate was evaporated to give the required starting material as a solid (0.561 g); NMR Spectrum: (DMSOd_6) 1.54 (t, 4H), 1.63 (m, 4H), 2.01 (s, 3H), 3.19 (t, 4H), 4.78 (s, 2H), 6.68 (m, 1H), 6.82 (d, 1H), 7.06 (m, 2H), 7.24 (m, 2H), 7.39 (s, 1H), 9.77 (s, 1H).

Example 52

N-[5-(3-fluoro-5-piperidinobenzamido)-2-methylphenyl]-3-piperidin-4-yloxybenzamide

Using an analogous procedure to that described in the first paragraph of Example 50, 3-(1-tert-butoxycarbonylpiperidin-4-yloxy)benzoic acid was reacted with N-(3-amino-4-methylphenyl)-3-fluoro-5-piperidinobenzamide to give N-[5-(3-fluoro-5-piperidinobenzamido)-2-methylphenyl]-3-(1-tert-butoxycarbonylpiperidin-4-yloxy)benzamide in 59% yield; NMR Spectrum: (DMSOd_6) 1.38 (s, 9H), 1.59 (m, 8H), 1.95 (m, 1H), 2.19 (s, 3H), 3.20 (m, 6H), 3.64 (m, 2H), 4.63 (m, 1H), 6.90 (d, 1H), 7.02 (d, 1H), 7.22 (m, 3H), 7.41 (t, 1H), 7.57 (m, 3H), 7.78 (s, 1H), 9.83 (s, 1H), 10.13 (s, 1H); Mass Spectrum: $M+H^+$ 631.

The product so obtained was treated with trifluoroacetic acid using an analogous procedure to that described in the second paragraph of Example 50. There was thus obtained the title compound in 72% yield; NMR Spectrum: (DMSOd_6) 1.41 (m, 2H), 1.59 (m, 8H), 1.9 (m, 1H), 2.19 (s, 3H), 2.58 (m, 2H), 2.96 (m, 2H), 3.24 (m, 4H), 4.43 (m, 1H), 6.9 (d, 1H), 7.02 (d, 1H), 7.17 (d, 1H), 7.21 (d, 1H), 7.27 (s, 1H), 7.41 (t, 1H), 7.57 (m, 3H), 7.78 (s, 1H), 9.83 (s, 1H), 10.13 (s, 1H); Mass Spectrum: $M+H^+$ 531.

The N-(3-amino-4-methylphenyl)-3-fluoro-5-piperidinobenzamide used as a starting material was obtained as follows :-

A mixture of N-(4-methyl-3-nitrophenyl)-3,5-difluorobenzamide (1 g) and piperidine (5 ml) was stirred and heated to 100°C for 36 hours. The reaction mixture was cooled and partitioned between ethyl acetate and water. The organic phase was washed with a saturated aqueous sodium chloride solution, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography on silica using a 7:3 mixture of isohexane and ethyl acetate as

eluent. There was thus obtained N-(4-methyl-3-nitrophenyl)-3-fluoro-5-piperidinobenzamide as a solid (1.12 g); NMR Spectrum: ($DMSOd_6$) 1.78 (m, 6H), 2.5 (s, 3H), 3.18 (t, 4H), 6.62 (m, 1H), 6.75 (m, 1H), 7.09 (d, 1H), 7.23 (d, 1H), 7.78 (m, 1H), 7.82 (s, 1H), 8.18 (d, 1H).

A portion (0.8 g) of the compound so obtained was dissolved in ethanol (80 ml) and hydrogenated over 10% palladium-on-carbon catalyst (0.1 g) under an atmosphere of hydrogen until the uptake of hydrogen ceased. The catalyst was removed by filtration and the filtrate was evaporated. The residue was triturated under ethyl acetate to give the required starting material (0.48 g); NMR Spectrum: ($DMSOd_6$) 1.56 (m, 6H), 2.0 (s, 3H), 3.21 (t, 4H), 4.78 (s, 2H), 6.76 (m, 1H), 6.82 (d, 1H), 6.84 (m, 1H), 6.98 (d, 1H), 7.03 (d, 1H), 7.22 (s, 1H), 9.80 (s, 1H); Mass Spectrum: $M+H^+$ 328.

Example 53

N-[2-methyl-5-(3-pyrrolidin-1-ylbenzamido)phenyl]-3-piperidin-4-yloxybenzamide

Using an analogous procedure to that described in the first paragraph of Example 25, 3-(1-tert-butoxycarbonylpiperidin-4-yloxy)benzoic acid was reacted with N-(3-amino-4-methylphenyl)-3-pyrrolidin-1-ylbenzamide to give N-[2-methyl-5-(3-pyrrolidin-1-ylbenzamido)phenyl]-3-(1-tert-butoxycarbonylpiperidin-4-yloxy)benzamide in 69% yield; NMR Spectrum: ($DMSOd_6$) 1.39 (s, 9H), 1.56 (m, 2H), 1.87 (m, 2H), 3.2 (m, 2H), 3.64 (m, 2H), 4.62 (m, 1H), 6.69 (d, 1H), 7.02 (s, 1H), 7.2 (m, 4H), 7.42 (t, 1H), 7.56 (m, 3H), 7.79 (s, 1H), 9.83 (s, 1H), 10.05 (s, 1H); Mass Spectrum: $M+H^+$ 599.

The product so obtained was treated with trifluoroacetic acid using an analogous procedure to that described in the second paragraph of Example 25. The reaction mixture was evaporated and the residue was triturated under diethyl ether. The solid so obtained was dissolved in water (50 ml) and the solution was basified by the addition of 1N aqueous sodium hydroxide solution. The resultant solid was isolated and dried. There was thus obtained the title compound in 62% yield; NMR Spectrum: ($DMSOd_6$) 1.46 (m, 2H), 1.94 (m, 4H), 2.19 (s, 3H), 2.6 (m, 2H), 2.98 (m, 2H), 3.3 (m, 4H), 4.48 (m, 1H), 6.68 (d, 1H), 7.02 (s, 1H), 7.2 (m, 4H), 7.4 (m, 1H), 7.56 (m, 3H), 7.8 (s, 1H), 9.83 (s, 1H), 10.05 (s, 1H); Mass Spectrum: $M+H^+$ 499.

The N-(3-amino-4-methylphenyl)-3-pyrrolidin-1-ylbenzamide used as a starting material was obtained as follows :-

A mixture of pyrrolidine (7.1 g), 3-fluorobenzonitrile (2.23 g) and DMSO (25 ml) was stirred and heated to 100°C for 20 hours. The mixture was allowed to cool to ambient temperature and was partitioned between diethyl ether and water. The organic phase was washed with a saturated aqueous sodium chloride solution, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography on silica using a 9:1 mixture of isohexane and ethyl acetate as eluent.. There was thus obtained 3-pyrrolidin-1-ylbenzonitrile as a solid (1.94 g); NMR Spectrum: ($CDCl_3$) 2.03 (t, 4H), 3.23 (t, 4H), 6.7 (m, 2H), 6.86 (t, 1H), 7.21 (d, 1H).

A mixture of a portion (1.23 g) of the material so obtained, 5N aqueous sodium hydroxide solution (10 ml) and n-butanol (8 ml) was stirred and heated to reflux for 20 hours. The mixture was evaporated. 1N aqueous hydrochloric acid (50 ml) was added followed by sufficient of a saturated aqueous sodium bicarbonate solution to bring the mixture to pH6. The solid was collected and dried to give 3-pyrrolidin-1-ylbenzoic acid (1.8 g); NMR Spectrum: ($DMSOd_6$) 1.93 (t, 4H), 3.21 (t, 4H), 6.85 (m, 1H), 7.07 (d, 1H), 7.18 (d, 1H), 7.22 (t, 1H).

A mixture of the material so obtained, oxalyl chloride (0.93 ml), DMF (3 drops) and methylene chloride (80 ml) was stirred at ambient temperature for 4 hours. The resultant mixture was evaporated. The material so obtained was dissolved in methylene chloride (80 ml) and added to a stirred mixture of 4-methyl-3-nitroaniline (1.14 g), triethylamine (2.19 ml) and methylene chloride (80 ml). The mixture was stirred at ambient temperature for 18 hours. The mixture was then washed in turn with water, with a saturated aqueous sodium bicarbonate solution and with water, dried ($MgSO_4$) and evaporated. The residue was triturated under diethyl ether. There was thus obtained N-(4-methyl-3-nitrophenyl)-3-pyrrolidin-1-ylbenzamide as a solid (1.24 g); NMR Spectrum: ($DMSOd_6$) 1.95 (t, 4H), 2.43 (s, 3H), 3.23 (t, 4H), 6.73 (m, 1H), 7.02 (s, 1H), 7.17 (d, 1H), 7.26 (t, 1H), 7.42 (d, 1H), 7.98 (m, 1H), 8.52 (d, 1H), 11.83 (s, 1H).

A mixture of the material so obtained, 10% palladium-on-carbon catalyst (0.15 g) and methanol (150 ml) was stirred under an atmosphere pressure of hydrogen at ambient temperature for 48 hours. The catalyst was filtered off and the filtrate was evaporated. The residue was triturated under diethyl ether to give the required starting material as a solid (0.5 g); NMR Spectrum: ($DMSOd_6$) 1.95 (m, 4H), 2.0 (s, 3H), 3.27 (m, 4H), 4.77 (s, 2H), 6.65

(m, 1H), 6.8 (m, 2H), 6.99 (s, 1H), 7.1 (m, 2H), 7.23 (m, 1H), 9.7 (s, 1H); Mass Spectrum: $M+H^+$ 296.

Example 54

N-[2-methyl-5-(3-morpholinobenzamido)phenyl]-3-pyrrolidin-3-yloxybenzamide

Using an analogous procedure to that described in the first paragraph of Example 25, 3-(1-tert-butoxycarbonylpyrrolidin-3-yloxy)benzoic acid was reacted with N-(3-amino-4-methylphenyl)-3-morpholinobenzamide to give N-[2-methyl-5-(3-morpholinobenzamido)phenyl]-3-(1-tert-butoxycarbonylpyrrolidin-3-yloxy)benzamide in 58% yield; NMR Spectrum: ($DMSOd_6$) 1.38 (s, 9H), 2.1 (m, 2H), 2.18 (s, 3H), 3.18 (t, 4H), 3.35 (m, 1H), 3.41 (m, 2H), 3.75 (t, 4H), 5.1 (m, 1H), 7.12 (td, 1H), 7.21 (d, 1H), 7.37 (m, 3H), 7.41 (t, 2H), 7.5 (s, 1H), 7.57 (d, 1H), 7.78 (d, 1H), 9.83 (s, 1H), 10.1 (s, 1H); Mass Spectrum: $M+H^+$ 601.

The product so obtained was treated with trifluoroacetic acid using an analogous procedure to that described in the second paragraph of Example 25. There was thus obtained the title compound in 66% yield; NMR Spectrum: ($DMSOd_6$) 1.9 (m, 2H), 2.12 (s, 3H), 2.85 (m, 2H), 3.12 (t, 4H), 3.41 (m, 2H), 3.72 (t, 4H), 4.9 (m, 1H), 7.08 (m, 2H), 7.21 (d, 1H), 7.35 (m, 3H), 7.52 (m, 3H), 7.63 (m, 1H), 7.72 (m, 1H), 9.92 (s, 1H), 10.21 (s,1H); Mass Spectrum: $M+H^+$ 501.

The 3-(1-tert-butoxycarbonylpyrrolidin-3-yloxy)benzoic acid used as a starting material was obtained as follows :-

Using an analogous procedure to that described in the first paragraph of the portion of Example 25 which is concerned with the preparation of starting materials, N-tert-butoxycarbonyl-3-hydroxypyrrolidine (J. Amer. Chem. Soc., 1982, 104, 5852-5853) was reacted with ethyl 3-hydroxybenzoate. The product so obtained was hydrolysed with sodium hydroxide using an analogous procedure to that described in the second paragraph of the portion of Example 25 which is concerned with the preparation of starting materials. There was thus obtained the required starting material; NMR Spectrum: ($DMSOd_6$) 1.38 (s, 9H), 2.06 (m, 2H), 3.1 (m, 3H), 3.55 (m, 1H), 5.03 (broad s, 1H), 7.18 (m, 1H), 7.38 (m,2H), 7.52 (d, 1H); Mass Spectrum: $M+H^+$ 308.

Example 55

N-[2-methyl-5-(3-morpholinobenzamido)phenyl]-4-piperidin-4-yloxybenzamide

Using an analogous procedure to that described in the first paragraph of Example 25, 4-(1-tert-butoxycarbonylpiperidin-4-yloxy)benzoic acid was reacted with N-(3-amino-4-methylphenyl)-3-morpholinobenzamide. The crude reaction product was purified by column chromatography on silica using increasingly polar mixtures of isohexane and ethyl acetate as eluent. There was thus obtained N-[2-methyl-5-(3-morpholinobenzamido)phenyl]-4-(1-tert-butoxycarbonylpiperidin-4-yloxy)benzamide in 51% yield; Mass Spectrum: $M+H^+$ 615.

The product so obtained was treated with trifluoroacetic acid using an analogous procedure to that described in the second paragraph of Example 25. The reaction product was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride and methanol as eluent. There was thus obtained the title compound in 62% yield; NMR Spectrum: ($DMSOd_6$) 1.53 (m, 2H), 1.95 (m, 2H), 2.16 (s, 3H), 2.7 (m, 2H), 3.03 (m, 2H), 3.18 (t, 4H), 3.73 (t, 4H), 4.57 (m, 1H), 7.05 (d, 2H), 7.13 (m, 1H), 7.2 (d, 2H), 7.35 (m, 2H), 7.44 (d, 1H), 7.56 (m, 1H), 7.79 (d, 1H), 7.94 (d, 2H), 9.7 (s, 1H), 10.1 (s, 1H); Mass Spectrum: $M+H^+$ 515.

The 4-(1-tert-butoxycarbonylpiperidin-4-yloxy)benzoic acid used as a starting material was obtained as follows :-

Using an analogous procedure to that described in the first paragraph of the portion of Example 25 which is concerned with the preparation of starting materials, N-tert-butoxycarbonyl-4-hydroxypiperidine was reacted with ethyl 4-hydroxybenzoate and the crude reaction product was purified by column chromatography on silica using increasingly polar mixtures of methylene chloride and methanol as eluent. The product so obtained was hydrolysed with sodium hydroxide using an analogous procedure to that described in the second paragraph of the portion of Example 25 which is concerned with the preparation of starting materials. There was thus obtained the required starting material; NMR Spectrum: ($DMSOd_6$) 1.38 (s, 9H), 1.51 (m, 2H), 1.9 (m, 2H), 3.15 (m, 2H), 3.64 (m, 2H), 4.65 (m, 1H), 7.03 (d, 2H), 7.84 (d, 2H); Mass Spectrum: $M+H^+$ 322.

Example 56

N-[2-methyl-5-(3-morpholinobenzamido)phenyl]-4-tetrahydrofuran-3-yloxybenzamide

Di-isopropyl azodicarboxylate (0.21 ml) was added to a stirred mixture of N-[2-methyl-5-(3-morpholinobenzamido)phenyl]-4-hydroxybenzamide (0.15 g), 3-hydroxytetrahydrofuran (0.31 g), triphenyl phosphine (0.275 g) and methylene chloride (5 ml) which had been cooled to 5°C. The resultant mixture was stirred at ambient temperature for 18 hours. The mixture was poured onto a pre-wetted (methylene chloride) ion-exchange column (isolute SCX 5 g column from International Sorbent Technology Limited) and eluted in turn with methylene chloride (40 ml), with methylene chloride (40 ml) containing 20% methanol and with methylene chloride containing 20% methanol and 3% of a saturated aqueous ammonium hydroxide solution. The product so obtained was further purified by column chromatography on silica using a 4:1 mixture of ethyl acetate and methanol as eluent. There was thus obtained the title compound as a solid (0.52 g); Mass Spectrum: $M+H^+$ 502.

Example 57

N-(5-{3-[N-(2-methoxyethyl)-N-methylamino]benzamido}-2-methylphenyl)-3-piperidin-4-yloxybenzamide

Using an analogous procedure to that described in the first paragraph of Example 25, 3-(1-tert-butoxycarbonylpiperidin-4-yloxy)benzoic acid was reacted with N-(3-amino-4-methylphenyl)-3-[N-(2-methoxyethyl)-N-methylamino]benzamide. The crude reaction product was purified by column chromatography on silica using increasingly polar mixtures of isohexane and ethyl acetate as eluent. There was thus obtained N-(5-{3-[N-(2-methoxyethyl)-N-methylamino]benzamido}-2-methylphenyl)-3-(1-tert-butoxycarbonylpiperidin-4-yloxy)benzamide in 63% yield; NMR Spectrum: ($DMSOd_6$) 1.38 (s, 9H), 1.54 (m, 2H), 2.19 (s, 3H), 2.96 (s, 3H), 3.2 (m, 5H), 3.5 (m, 4H), 3.65 (m, 2H), 4.63 (m, 1H), 6.88 (d, 1H), 7.2 (m, 5H), 7.41 (t, 3H), 7.57 (m, 3H), 7.79 (s, 1H), 9.83 (s, 1H), 10.06 (s, 1H); Mass Spectrum: $M-C_3H_7^+$ 561.

The product so obtained was treated with trifluoroacetic acid using an analogous procedure to that described in the second paragraph of Example 25. The reaction product was purified by column chromatography on silica using increasingly polar mixtures of methylene

chloride and methanol as eluent. There was thus obtained the title compound in 62% yield; NMR Spectrum: ($DMSOd_6$) 1.53 (m, 2H), 1.95 (m, 2H), 2.16 (s, 3H), 2.7 (m, 2H), 3.03 (m, 2H), 3.18 (t, 4H), 3.73 (t, 4H), 4.57 (m, 1H), 7.05 (d, 2H), 7.13 (m, 1H), 7.2 (d, 2H), 7.35 (m, 2H), 7.44 (d, 1H), 7.56 (m, 1H), 7.79 (d, 1H), 7.94 (d, 2H), 9.7 (s, 1H), 10.1 (s, 1H); Mass Spectrum: $M+H^+$ 515.

The N-(3-amino-4-methylphenyl)-3-[N-(2-methoxyethyl)-N-methylamino]benzamide used as a starting material was obtained as follows :-

A mixture of 3-bromobenzonitrile (3.64 g), (S)-(-)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (0.279 g), tris(dibenzylidineacetone)dipalladium(0) (0.274 g) sodium tert-butoxide (3.86 g), and toluene (25 ml) was stirred at ambient temperature for 2 minutes. N-(2-methoxyethyl)-N-methylamine (2.57 ml) was added and the resultant mixture was stirred and heated to reflux for 18 hours. The mixture was cooled and partitioned between toluene and water. The organic phase was washed with a saturated aqueous sodium chloride solution, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography using a 9:1 mixture of isohexane and ethyl acetate as eluent. There was thus obtained 3-[N-(2-methoxyethyl)-N-methylamino]benzonitrile (2.51 g); NMR Spectrum: ($CDCl_3$) 2.98 (s, 3H), 3.36 (s, 3H), 3.5 (t, 4H), 6.9 (m, 3H), 7.23 (m, 1H).

A mixture of the material so obtained, 10N aqueous sodium hydroxide solution (6.5 ml), water (6.5 ml) and n-butanol (15 ml) was stirred and heated to reflux for 28 hours. The mixture was evaporated and the residue was partitioned between methylene chloride and dilute aqueous hydrochloric acid. The organic extracts were dried ($MgSO_4$) and evaporated to leave an oil which on tituration under isohexane formed a solid. There was thus obtained 3-[N-(2-methoxyethyl)-N-methylamino]benzoic acid (1.42 g); NMR Spectrum: ($DMSOd_6$) 2.9 (s, 3H), 3.22 (m, 3H), 3.43 (m, 4H), 6.92 (m, 1H), 7.2 (m, 3H).

A mixture of the material so obtained, oxalyl chloride (0.67 ml) and methylene chloride (70 ml) was stirred at ambient temperature for 3 hours. The resultant mixture was evaporated. The material so obtained was dissolved in methylene chloride (70 ml) and added to a stirred mixture of 4-methyl-3-nitroaniline (0.82 g), triethylamine (1.58 ml) and methylene chloride (70 ml). The mixture was stirred at ambient temperature for 18 hours. The mixture was then washed in turn with water, with a saturated aqueous sodium bicarbonate solution and with water, dried ($MgSO_4$) and evaporated. The residue was purified by column

chromatography on silica using increasingly polar mixtures of methylene chloride and methanol as eluent. There was thus obtained N-(4-methyl-3-nitrophenyl)-3-[N-(2-methoxyethyl)-N-methylamino]benzamide as a solid (1.11 g); NMR Spectrum: ($DMSOd_6$) 2.98 (s, 3H), 2.45(s, 3H), 3.4 (s, 3H), 3.52 (m, 4H), 6.91 (d, 1H), 7.18 (s, 2H), 7.26 (t, 1H), 7.43 (d, 1H), 7.98 (m, 1H), 8.52 (s, 1H), 10.41 (s, 1H).

A mixture of the material so obtained, 10% palladium-on-carbon catalyst (0.15 g) and methanol (150 ml) was stirred under an atmosphere pressure of hydrogen at ambient temperature for 18 hours. The catalyst was filtered off and the filtrate was evaporated. There was thus obtained the required starting material as a solid (0.86 g); NMR Spectrum: ($DMSOd_6$) 2.0 (s, 3H), 2.96 (s, 3H), 3.25 (s, 3H), 3.51 (m, 4H), 4.79 (s, 2H), 6.82 (m, 3H), 7.1 (m, 3H), 7.23 (m, 1H), 9.73 (s, 1H); Mass Spectrum: $M+H^+$ 314.

Example 58

N-(5-{3-[N-(2-methoxyethyl)-N-methylamino]benzamido}-2-methylphenyl)-3-pyrrolidin-3-yloxybenzamide

Using an analogous procedure to that described in the first paragraph of Example 25, 3-(1-tert-butoxycarbonylpyrrolidin-3-yloxy)benzoic acid was reacted with N-(3-amino-4-methylphenyl)-3-[N-(2-methoxyethyl)-N-methylamino]benzamide to give N-(5-{3-[N-(2-methoxyethyl)-N-methylamino]benzamido}-2-methylphenyl)-3-(1-tert-butoxycarbonylpyrrolidin-3-yloxy)benzamide in 59% yield; NMR Spectrum: ($DMSOd_6$) 1.39 (s, 9H), 2.08 (m, 2H), 2.18 (s, 3H), 2.96 (s, 3H), 3.22 (s, 3H),3.25 (m, 2H), 3.52 (m, 6H), 5.07 (s, 1H), 6.87 (d, 1H), 7.2 (m, 5H), 7.43 (t, 1H), 7.55 (m, 3H), 7.79 (s, 1H), 9.86 (s, 1H), 10.06 (s, 1H); Mass Spectrum: $M-C_3H_7^+$ 547.

The product so obtained was treated with trifluoroacetic acid using an analogous procedure to that described in the second paragraph of Example 25. There was thus obtained the title compound in 26% yield; NMR Spectrum: ($DMSOd_6$) 1.77 (m, 1H), 2.02 (m, 1H), 2.18 (s, 3H), 2.78 (m, 2H), 2.95 (s, 3H), 3.06 (m, 2H), 4.92 (m, 4H), 6.87 (d, 1H), 7.2 (m, 5H), 7.47 (m, 4H), 7.79 (s, 1H), 9.84 (s, 1H), 10.06 (s, 1H); Mass Spectrum: $M+H^+$ 503.

Example 59

N-(5-{3-[N-(2-methoxyethyl)-N-methylamino]benzamido}-2-methylphenyl)-3-(4-methylpiperazin-1-ylmethyl)benzamide

A mixture of N-methylpiperazine (3 ml) and N-(5-{3-[N-(2-methoxyethyl)-N-methylamino]benzamido}-2-methylphenyl)-3-chloromethylbenzamide (0.21 g) was stirred and heated to 80°C for 3 hours. The mixture was cooled to ambient temperature and partitioned between ethyl acetate and water. The organic phase was evaporated and the residue was triturated under diethyl ether. There was thus obtained the title compound (0.17 g); NMR Spectrum: ($DMSOd_6$) 2.17 (d, 6H), 2.33 (m, 8H), 2.98 (s, 3H), 3.23 (s, 3H), 3.50 (m, 6H), 6.87 (d, 1H), 7.2 (m, 4H), 7.46 (m, 2H), 7.57 (m, 1H), 7.8 (s, 1H), 7.86 (m, 2H), 9.87 (s, 1H), 10.06 (s, 1H); Mass Spectrum: $M+H^+$ 530.

The N-(5-{3-[N-(2-methoxyethyl)-N-methylamino]benzamido}-2-methylphenyl)-3-chloromethylbenzamide used as a starting material was obtained as follows :-

Using an analogous procedure to that described in Example 37, 3-chloromethylbenzoyl chloride was reacted with N-(3-amino-4-methylphenyl)-3-[N-(2-methoxyethyl)-N-methylamino]benzamide. The reaction mixture was washed in turn with water, and a saturated aqueous sodium bicarbonate solution, dried ($MgSO_4$) and evaporated. The residue purified by column chromatography on silica using increasingly polar mixtures of isohexane and ethyl acetate as eluent. There was thus obtained the required starting material as a solid in 74% yield which was used without further purification.

Example 60

N-[2-methyl-5-(3-morpholinobenzamido)phenyl]-3-methanesulphonylaminobenzamide

Methanesulphonyl chloride (0.16 ml) was added to a stirred mixture of N-[2-methyl-5-(3-morpholinobenzamido)phenyl]-3-aminobenzamide (0.765 g), pyridine (0.29 ml) and methylene chloride (30 ml) and the resultant mixture was stirred at ambient temperature for 18 hours. A second portion (0.158 ml) of methanesulphonyl chloride was added and the resultant mixture was stirred at ambient temperature for a further 18 hours. The reaction mixture was washed with water, dried ($MgSO_4$) and evaporated. The residue was triturated under diethyl ether. The solid so obtained was dried under vacuum at 60°C. There was thus obtained the title compound (0.97 g); NMR Spectrum: ($DMSOd_6$) 2.2 (s, 3H), 3.03

(s, 3H), 3.2 (t, 4H), 3.74 (t, 4H), 7.17 (m, 1H), 7.23 (d, 1H), 7.4 (m, 5H), 7.59 (m, 1H), 7.7 (d, 1H), 7.8 (m, 2H), 9.93 (d, 2H), 10.14 (s, 1H); Mass Spectrum: $M+H^+$ 509.

The N-[2-methyl-5-(3-morpholinobenzamido)phenyl]-3-aminobenzamide used as a starting material was prepared as follows :-

3-Nitrobenzoyl chloride (1.31 g) was added to a mixture of N-(3-amino-4-methylphenyl)-3-morpholinobenzamide (2 g), triethylamine (1.79 ml) and methylene chloride (40 ml) and the resultant mixture was stirred at ambient temperature for 18 hours. The precipitate was isolated, washed in turn with methylene chloride and diethyl ether and dried under vacuum at 60°C. There was thus obtained N-[2-methyl-5-(3-morpholinobenzamido)phenyl]-3-nitrobenzamide (0.95 g); m.p. 247-248°C; NMR Spectrum: ($DMSOd_6$) 2.22 (s, 3H), 3.2 (t, 4H), 3.75 (t, 4H), 7.13 (m, 1H), 7.24 (d, 1H), 7.35 (m, 2H), 7.44 (d, 1H), 7.59 (m, 1H), 7.84 (m, 2H), 8.43 (m, 2H), 8.79 (d, 1H), 10.13 (s, H), 10.3 (s, 1H); Mass Spectrum: $M-H^-$ 459.

10% Palladium-on-carbon (0.13 g) was added to a solution of the material so obtained in methanol (150 ml) and the mixture was stirred under an atmosphere of hydrogen. After cessation of hydrogen uptake, the catalyst was removed by filtration and the filtrate was evaporated. The residue was dried under vacuum at 60°C. There was thus obtained the required starting material (0.77 g); m.p. 171-172°C; NMR Spectrum: ($DMSOd_6$) 2.18 (s, 3H), 3.14 (t, 4H), 3.26 (s, 2H), 3.73 (t, 4H), 6.72 (m,1H), 7.11 (m, 4H), 7.19 (d, 1H), 7.35 (m, 2H), 7.43 (d, 1H), 7.56 (m , 1H); 7.76 (d, 1H), 9.63 (s, 1H), 10.1 (s, 1H); Mass Spectrum: $M+H^+$ 431.

Example 61

N-[2-methyl-5-(3-morpholinobenzamido)phenyl]-3-(N-methylmethanesulphonylamino)benzamide

Methyl iodide (0.023 ml) was added to a mixture of N-[2-methyl-5-(3-morpholinobenzamido)phenyl]-3-methanesulphonylaminobenzamide (0.17 g), caesium carbonate (0.121 g) and DMF (10 ml) and the resultant mixture was stirred and heated to 50°C for 72 hours. The reaction mixture was poured into water (200 ml). The precipitate was isolated, washed in turn with water and diethyl ether and dried under vacuum at 60°C. There was thus obtained the title compound (0.1 g); m.p. 208-209°C; NMR Spectrum: ($DMSOd_6$)

2.19 (s, 3H), 3.0 (s, 3H), 3.18 (t, 4H), 3.75 (t, 4H), 7.13 (m, 1H), 7.23 (d, 1H), 7.36 (m, 2H), 7.45 (d, 1H), 7.59 (m , 3H), 7.81 (d, 1H), 7.91 (d, 1H), 7.99 (d, 1H), 9.98 (s, 1H), 10.12 (s, 1H); Mass Spectrum: $M+H^+$ 523.

Example 62

N-[2-methyl-5-(3-morpholinobenzamido)phenyl]-3-(N-ethylmethanesulphonylamino)benzamide

Using an analogous procedure to that described in Example 61, N-[2-methyl-5-(3-morpholinobenzamido)phenyl]-3-methanesulphonylaminobenzamide was reacted with ethyl iodide to give the title compound in 64% yield; m.p. 192-193°C; NMR Spectrum: ($DMSOd_6$) 1.05 (t, 3H), 2.21 (s, 3H), 3.16 (t, 4H), 3.73 (m, 6H), 7.13 (m, 1H), 7.23 (d, 1H), 7.36 (m, 2H), 7.43 (d, 1H), 7.58 (m , 3H), 7.81 (d, 1H), 7.95 (m , 2H), 7.99 (d, 1H), 10.0 (s, 1H), 10.12 (s, 1H); Mass Spectrum: $M+H^+$ 537.

Example 63

N-[5-(3-dimethylaminobenzamido)-2-methylphenyl]-3-chloromethylbenzamide

Triethylamine (1.55 ml) was added to a stirred mixture of N-(3-amino-4-methylphenyl)-3-dimethylaminobenzamide (3.0 g), 3-chloromethylbenzoyl chloride (2.76 g) and methylene chloride (50 ml) and the reaction mixture was stirred at ambient temperature for 16 hours. The mixture was evaporated and the residue was triturated under water. The solid so obtained was isolated, washed in turn with a saturated aqueous sodium bicarbonate solution, water and isohexane and dried under vacuum at 55°C. There was thus obtained the title compound (4.8 g); NMR Spectrum: ($DMSOd_6$) 2.19 (s, 3H), 2.96 (s, 6H), 4.84 (s, 2H), 6.9 (d, 1H), 7.26 (m, 3H), 7.5-7.7 (m, 3H), 7.8-8.1 (m, 4H), 9.97 (s, 1H), 10.09 (s, 1H); Mass Spectrum: $M-H^-$ 420.

Example 64

N-[5-(3-dimethylaminobenzamido)-2-methylphenyl]-4-chloromethylbenzamide

4-Chloromethylbenzoyl chloride was reacted with N-(3-amino-4-methylphenyl)-3-dimethylaminobenzamide using an analogous procedure to that described in Example 37 except that the reaction product was triturated under water rather than under 2N aqueous

hydrochloric acid solution. There was thus obtained the title compound; NMR Spectrum: ($DMSOd_6$) 2.19 (s, 3H), 2.95 (s, 6H), 4.28 (s, 2H), 6.9 (d, 1H), 7.21 (m, 3H), 7.29 (d, 1H), 7.58 (d, 3H), 7.8 (s, 1H), 7.96 (d, 2H), 9.9 (s, 1H), 10.08 (s, 1H); Mass Spectrum: $M-H^-$ 420.

Example 65

N-[2-methyl-5-(3-morpholinobenzamido)phenyl]-3-chloromethylbenzamide

Using an analogous procedure to that described in Example 63, 3-chloromethylbenzoyl chloride was reacted with N-(3-amino-4-methylphenyl)-3-morpholinobenzamide. There was thus obtained the title compound in 98% yield; NMR Spectrum: ($DMSOd_6$) 2.19 (s, 3H), 3.17 (m, 4H), 3.75 (m, 4H), 4.85 (s, 2H), 7.13 (d, 1H), 7.22 (d, 1H), 7.34 (m, 2H), 7.44 (s, 1H), 7.54 (m, 2H), 7.65 (d, 1H), 7.79 (s, 1H), 7.95 (d, 1H), 8.03 (s, 1H), 9.96 (s, 1H), 10.12 (s, 1H); Mass Spectrum: $M+H^+$ 464.

Example 66

N-[5-(4-fluoro-3-trifluoromethylbenzamido)-2-methylphenyl]-4-diethylaminomethylbenzamide

Oxalyl chloride (0.1 ml) was added to a stirred mixture of 4-fluoro-3-trifluoromethylbenzoic acid (0.2 g), DMF (3 drops) and methylene chloride (8 ml) and the mixture was stirred at ambient temperature for 3 hours. The solvent was evaporated. The residue was dissolved in pyridine (5 ml) and a solution of N-(5-amino-2-methylphenyl)-4-diethylaminomethylbenzamide (0.2 g) in methylene chloride (4 ml) was added. The resultant mixture was stirred at ambient temperature for 3 days. The mixture was evaporated and the residue was triturated under water. The resultant solid was washed with a saturated aqueous solution of sodium bicarbonate and dried under vacuum at 55°C to give the title compound (0.3 g); NMR Spectrum: ($DMSOd_6$) 1.23 (broad s, 6H), 2.21 (s, 3H), 3.03 (broad s, 4H), 3.3 (m, 2H), 7.26 (d, 1H), 7.58 (d, 1H), 7.7 (m, 3H), 7.82 (s, 1H), 8.04 (d, 2H), 8.35 (d, 2H), 9.96 (s, 1H), 10.48 (s, 1H); Mass Spectrum: $M+H^+$ 502.

Example 67

N-[5-(3-fluoro-5-morpholinobenzamido)-2-methylphenyl]-4-diethylaminomethylbenzamide

A mixture of N-[5-(3,5-difluorobenzamido)-2-methylphenyl]-4-diethylaminomethylbenzamide (0.069 g) and morpholine (3 ml) was stirred and heated to 100°C for 6 days. The mixture was cooled to ambient temperature and poured into water. The resultant solid was isolated, washed in turn with water and diethyl ether and dried under vacuum at 40°C. There was thus obtained the title compound (0.033 g); NMR Spectrum: ($DMSOd_6$) 0.98 (t, 6H), 2.2 (s, 3H), 2.46-2.49 (m, 4H), 3.20-3.24 (m, 4H), 3.58 (s, 2H), 3.72-3.75 (m, 4H), 6.95 (d, 1H), 7.14 (d, 1H), 7.21 (d, 1H), 7.3 (s, 1H), 7.45 (s, 2H), 7.58 (d, 1H), 7.78 (s, 1H), 7.91 (d, 2H), 9.82 (s, 1H), 10.15 (s, 1H); Mass Spectrum: $M+H^+$ 519.

The N-[5-(3,5-difluorobenzamido)-2-methylphenyl]-4-diethylaminomethylbenzamide used as a starting material was obtained as follows :-

3,5-Difluorobenzoyl chloride (0.088 g) was added to a stirred mixture of N-(5-amino-2-methylphenyl)-4-diethylaminomethylbenzamide (0.14 g), triethylamine (0.12 g) and methylene chloride (5 ml) and the mixture was stirred at ambient temperature for 16 hours. The mixture was washed with a saturated aqueous sodium bicarbonate solution. The organic phase was evaporated and the residue was triturated under a mixture of ethyl acetate and diethyl ether. There was thus obtained the required starting material (0.115 g); NMR Spectrum: ($DMSOd_6$) 0.98 (t, 6H), 2.2 (s, 3H), 2.43-2.49 (m, 4H), 3.59 (s, 2H), 7.24 (d, 1H), 7.43-58 (m, 4H), 7.68 (d, 2H), 7.81 (s, 1H), 7.92 (d, 2H), 9.83 (s, 1H), 10.44 (s, 1H); Mass Spectrum: $M+H^+$ 452.

Example 68

N-[5-(3-fluoro-5-pyrrolidin-1-ylbenzamido)-2-methylphenyl]-4-diethylaminomethylbenzamide

Using an analogous procedure to that described in Example 67 except that the reaction mixture was heated to 100°C for 16 hours rather than for 6 days, N-[5-(3,5-difluorobenzamido)-2-methylphenyl]-4-diethylaminomethylbenzamide was reacted with pyrrolidine. There was thus obtained the title compound in 81% yield; NMR Spectrum: ($DMSOd_6$) 0.98 (t, 6H), 1.95-2.0 (m, 4H), 2.2 (s, 3H), 2.4-2.5 (m, 4H), 3.3 (m, 4H), 3.6 (s,

2H), 6.4-6.5 (m, 1H), 6.85-6.95 (m, 2H), 7.2 (d, 2H), 7.45 (d, 2H), 7.58 (m, 1H), 7.8 (m, 1H), 7.95 (d, 2H), 9.8 (s, 1H), 10.1 (broad s, 1H); Mass Spectrum: $M+H^+$ 503.

Example 69

N-[5-(3-fluoro-5-piperidinobenzamido)-2-methylphenyl]-4-diethylaminomethylbenzamide

Using an analogous procedure to that described in Example 67 except that the reaction mixture was heated to 100°C for 16 hours rather than for 6 days, N-[5-(3,5-difluorobenzamido)-2-methylphenyl]-4-diethylaminomethylbenzamide was reacted with piperidine. There was thus obtained the title compound in 83% yield; NMR Spectrum: ($DMSOd_6$) 0.98 (t, 6H), 1.3-1.7 (m, 8H), 2.2 (s, 3H), 2.4-2.5 (m, 2H), 3.2-3.4 (m, 4H), 6.85-6.95 (m, 1H), 7.0-7.1 (m, 1H), 7.2-7.3 (m, 2H), 7.45 (d, 2H), 7.5-7.6 (m, 1H), 7.8 (m, 1H), 7.9 (d, 2H), 9.8 (s, 1H), 10.13 (broad s, 1H); Mass Spectrum: $M+H^+$ 517.

Example 70

N-[2-methyl-5-(5-morpholino-2-nitrobenzamido)phenyl]-4-diethylaminomethylbenzamide

Using an analogous procedure to that described in Example 67 except that the reaction mixture was heated to 105°C for 16 hours rather than to 100°C for 6 days, N-[5-(5-chloro-2-nitrobenzamido)-2-methylphenyl]-4-diethylaminomethylbenzamide was reacted with morpholine. The solid so obtained was dissolved in methylene chloride and the solution was washed with a saturated aqueous sodium bicarbonate solution. The organic solution was dried ($MgSO_4$) and evaporated. There was thus obtained the title compound in 64% yield; NMR Spectrum: ($DMSOd_6$) 0.98 (t, 6H), 2.2 (s, 3H), 2.4-2.6 (m, 4H), 3.4-3.5 (m, 4H), 3.6 (s, 2H), 3.7-3.8 (m, 4H), 7.0-7.1 (m, 2H), 7.2 (m, 1H), 7.4-7.5 (m, 2H), 7.7 (m, 1H), 7.9 (d, 2H), 8.05 (d, 1H), 9.85 (s, 1H), 10.38 (broad s, 1H); Mass Spectrum: $M+H^+$ 546.

The N-[5-(5-chloro-2-nitrobenzamido)-2-methylphenyl]-4-diethylaminomethylbenzamide used as a starting material was obtained as follows :-

Using an analogous procedure to that described in the portion of Example 67 which is concerned with the preparation of starting materials, 5-chloro-2-nitrobenzoyl chloride (obtained by the reaction of 5-chloro-2-nitrobenzoic acid and oxalyl chloride) was reacted

with N-(5-amino-2-methylphenyl)-4-diethylaminomethylbenzamide to give the required starting material in 69% yield; Mass Spectrum: $M+H^+$ 495.

Example 71

N-[5-(2-amino-3-morpholinobenzamido)-2-methylphenyl]-4-diethylaminomethylbenzamide

A mixture of N-[2-methyl-5-(3-morpholino-2-nitrobenzamido)phenyl]-4-diethylaminomethylbenzamide (1.21 g), iron powder (1.24 g), glacial acetic acid (0.44 ml), water (2.2 ml) and ethanol (22.2 ml) was stirred and heated to 95°C for 9 hours. The resultant mixture was cooled to ambient temperature and basified to pH9 by the addition of a saturated aqueous sodium bicarbonate sokution. The mixture was filtered and the filtrate was evaporated. The residue was partitioned between ethyl acetate and a saturated aqueous sodium bicarbonate solution. The organic phase was dried ($MgSO_4$)and evaporated. There was thus obtained the title compound as a solid (0.826 g); Mass Spectrum: $M+H^+$ 516.

The N-[2-methyl-5-(3-morpholino-2-nitrobenzamido)phenyl]-4-diethylaminomethylbenzamide used as a starting material was obtained as follows :-

Using an analogous procedure to that described in the portion of Example 67 which is concerned with the preparation of starting materials, 3-chloro-2-nitrobenzoyl chloride (obtained by the reaction of 3-chloro-2-nitrobenzoic acid and oxalyl chloride) was reacted with N-(5-amino-2-methylphenyl)-4-diethylaminomethylbenzamide. There was thus obtained N-[5-(3-chloro-2-nitrobenzamido)-2-methylphenyl]-4-diethylaminomethylbenzamide in 55% yield; NMR Spectrum: ($DMSOd_6$) 0.98 (t, 6H), 2.2 (s, 3H), 2.4-2.5 (m, 4H), 3.6 (s, 2H), 7.2-7.25 (m, 1H), 7.4-7.45 (m, 3H), 7.7-7.8 (m, 2H), 7.9-8.0 (m, 4H), 9.8 (s, 1H); Mass Spectrum: $M+H^+$ 495.

Using an analogous procedure to that described in Example 67 except that the reaction mixture was heated to 100°C for 16 hours rather than for 6 days, N-[5-(3-chloro-2-nitrobenzamido)-2-methylphenyl]-4-diethylaminomethylbenzamide was reacted with morpholine. The solid so obtained was dissolved in methylene chloride and the solution was washed with a saturated aqueous sodium bicarbonate solution. The organic solution was dried ($MgSO_4$) and evaporated. There was thus obtained N-[2-methyl-5-(3-morpholino-2-nitrobenzamido)phenyl]-4-diethylaminomethylbenzamide in 73% yield; NMR Spectrum:

(DMSOd_6) 0.98 (t, 6H), 2.2 (s, 3H), 2.4-2.5 (m, 4H), 2.9-2.95 (m, 4H), 3.6 (s, 2H), 3.6-3.7 (m, 4H), 7.2-7.25 (m, 1H), 7.4-7.45 (m, 3H), 7.5-7.6 (m, 1H), 7.6-7.7 (m, 2H), 7.75 (m, 1H), 7.9-7.95 (d, 2H), 9.8 (s, 1H), 10.62 (broad s,1H); Mass Spectrum: M+H$^+$ 546.

Example 72

N-[5-(5-cyclohexylvaleramido)-2-methylphenyl]-4-(diethylaminomethyl)benzamide

Using an analogous procedure to that described in Example 22 except that the step of washing the reaction mixture with a 1M aqueous citric acid solution was omitted, N-(5-amino-2-methylphenyl)-4-diethylaminomethylbenzamide was reacted with 5-cyclohexylvaleryl chloride (obtained by the reaction of 5-cyclohexylvaleric acid and oxalyl chloride using a conventional procedure) to give the title compound; Mass Spectrum: M+H$^+$ 478.

Example 73

N-[2-methyl-5-(3-morpholinobenzamido)phenyl]-3-(N-methylhomopiperidin-4-yloxy)benzamide

As described hereinbefore in Example 7, 2-(2-chloroethyl)-N-methylpyrrolidine was reacted with N-[2-methyl-5-(3-morpholinobenzamido)phenyl]-3-hydroxybenzamide and the reaction product was purified by column chromatography on silica using a 9:1 mixture of methylene chloride and methanol as eluent. There was thus obtained N-[2-methyl-5-(3-morpholinobenzamido)phenyl]-3-[2-(N-methylpyrrolidin-2-yl)ethoxy]benzamide (Example 7, Compound No. 32). On further elution an isomeric by-product was obtained. There was thus obtained the title compound NMR Spectrum: (DMSOd_6) 1.6 (m, 1H), 1.79 (m, 3H), 2.04 (m, 2H), 2.17 (s, 3H), 2.24 (s, 3H), 2.52 (m, 4H), 3.18 (t, 4H), 3.76 (t, 4H), 4.66 (m, 1H), 7.1 (m, 2H), 7.21 (d, 1H), 7.4 (m, 4H), 7.5 (d, 1H), 7.56 (m, 1H), 7.78 (d, 1H), 9.83 (s 1H), 10.11 (s, 1H); Mass Spectrum: M+H$^+$ 543.

Example 74

N-{5-[3-fluoro-5-(3-pyrrolin-1-yl)benzamido]-2-methylphenyl}-4-diethylaminomethylbenzamide

Using an analogous procedure to that described in Example 67 except that the reaction

mixture was heated to 100°C for 16 hours rather than for 6 days, N-[5-(3,5-difluorobenzamido)-2-methylphenyl]-4-diethylaminomethylbenzamide was reacted with 3-pyrroline. There was thus obtained the title compound in 58% yield; NMR Spectrum: ($DMSOd_6$) 1.0 (t, 6H), 2.2 (s, 3H), 2.5 (m, 4H), 3.6 (s, 2H), 4.15 (s, 4H), 6.05 (m, 1H), 6.45-6.55 (m, 1H), 6.9 (s, 1H), 6.97 (m, 1H), 7.22 (m, 1H), 7.45 (d, 2H), 7.57 (m, 1H), 7.8 (m, 1H), 7.95 (d, 2H), 9.8 (s, 1H), 10.12 (broad s, 1H); Mass Spectrum: $M+H^+$ 501.

Example 75

N-[2-methyl-5-(3-morpholinobenzamido)phenyl]-3-tetrahydrofuran-3-yloxybenzamide

1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.165 g) was added to a stirred mixture of 3-(tetrahydrofuran-3-yloxy)benzoic acid (0.15 g), 1-hydroxybenzotriazole (0.146 g) and DMF (5 ml) which had been cooled to 0°C. The reaction mixture was stirred at 0°C for 5 minutes and a solution of N-(3-amino-4-methylphenyl)-3-morpholinobenzamide (0.224 g) in DMF (1 ml) was added. The reaction mixture was allowed to come to ambient temperature and was stirred for 16 hours. The reaction mixture was poured into water and the resultant solid was isolated and purified by column chromatography on silica using a 99:1 mixture of methylene chloride and methanol as eluent. There was thus obtained the title compound (o.228 g); NMR Spectrum: ($DMSOd_6$) 1.99 (m, 1H), 2.18 (s, 3H), 2.25 (m, 1H), 3.17 (t, 4H), 3.72 (t, 4H), 3.88 (m, 4H), 5.13 (m, 1H), 7.11 (m, 2H), 7.21 (d, 1H), 7.39 (m, 5H), 7.56 (m, 2H), 7.79 (m, 2H), 9.83 (s, 1H), 10.11 (s, 1H); Mass Spectrum: $M+H^+$ 502.

The 3-(tetrahydrofuran-3-yloxy)benzoic acid used as a starting material was obtained as follows :-

Diethyl azodicarboxylate (2.09 g) was added to a stirred mixture of ethyl 3-hydroxybenzoate (1.662 g), 3-hydroxytetrahydrofuran (0.881 g), triphenylphosphine (3.41 g) and THF (40 ml) which had been cooled to 0°C. The resultant mixture was allowed to warm to ambient temperature and was stirred for 18 hours. The mixture was evaporated and the residue was triturated under a 9:1 mixture of hexane and ethyl acetate. The solid triphenylphosphine oxide so formed was filtered off. The filtrate was evaporated and the residue was purified by column chromatography on silica using a 99:1 mixture of methylene chloride and methanol as eluent. There was thus obtained ethyl 3-(tetrahydrofuran-

3-yloxy)benzoate (1.56 g); NMR Spectrum: ($DMSOd_6$) 1.27 (t, 3H), 1.93 (m, 1H), 2.22 (m, 1H), 3.82 (m, 4H), 4.27 (m, 2H), 5.08 (m, 1H), 7.19 (m, 1H), 7.42 (m, 2H), 7.52 (d, 1H).

Sodium hydroxide solution (1N; 10.22 ml) was added to a solution in ethanol (20 ml) of the ester so obtained and the mixture was stirred at ambient temperature for 48 hours. The mixture was evaporated and the residue was partitioned between ethyl acetate and a 1N aqueous hydrochloric acid solution. The organic phase was washed with water, dried ($MgSO_4$) and evaporated to give the required starting material as a solid (0.3 g) NMR Spectrum: ($DMSOd_6$) 1.9 (m, 1H), 2.2 (m, 1H), 3.8 (m, 4H), 5.03 (m, 1H), 7.07 (m, 1H), 7.36 (t, 1H), 7.41 (s, 1H), 7.52 (d, 1H).

Example 76

N-[2-methyl-5-(3-morpholino-5-trifluoromethylbenzamido)phenyl]-3-piperidin-4-yloxybenzamide

Using an analogous procedure to that described in the first paragraph of Example 50, 3-(1-tert-butoxycarbonylpiperidin-4-yloxy)benzoic acid was reacted with N-(3-amino-4-methylphenyl)-3-morpholino-5-trifluoromethylbenzamide to give N-[2-methyl-5-(3-morpholino-5-trifluoromethylbenzamido)phenyl]-3-(1-tert-butoxycarbonylpiperidin-4-yloxy)benzamide in 77% yield; NMR Spectrum: ($DMSOd_6$) 1.37 (s, 9H), 1.55 (m, 2H), 1.95 (m, 2H), 2.19 (s, 3H), 3.2 (m, 2H), 3.25 (t, 4H), 3.63 (m, 2H), 3.77 (t, 4H), 4.63 (m, 1H), 7.18 (m, 1H), 7.22 (d, 1H), 7.37 (s, 1H), 7.41 (t, 1H), 7.5 (s, 2H), 7.57 (m, 1H), 7.62 (s, 1H), 7.7 (s, 1H), 7.78 (d, 1H), 9.83 (s, 1H), 10.31 (s, 1H); Mass Spectrum: $M+H^+$ 683.

The product so obtained was treated with trifluoroacetic acid using an analogous procedure to that described in the second paragraph of Example 50. There was thus obtained the title compound in 62% yield; NMR Spectrum: ($DMSOd_6$) 1.38 (m, 2H), 1.85 (m, 2H), 2.16 (s, 3H), 2.45 (m, 2H), 2.88 (m, 2H), 3.22 (t, 4H), 3.7 (t, 4H), 4.4 (s, 1H), 7.05 (d, 1H), 7.12 (d, 1H), 7.26 (s, 1H), 7.31 (t, 1H), 7.47 (m, 3H), 7.6 (s, 1H), 7.7 (d, 2H), 10.15 (m, 2H); Mass Spectrum: $M+H^+$ 583.

The N-(3-amino-4-methylphenyl)-3-morpholino-5-trifluoromethylbenzamide used as a starting material was obtained as follows :-

Ethyl 3-morpholino-5-trifluoromethylbenzoate was prepared from ethyl 3-fluoro-

5-trifluoromethylbenzoate by the method described by Brown *et al.*, Tetrahedron Lett., 1999, 40, 1219. The material so obtained compound gave the following data :- NMR Spectrum: ($CDCl_3$) 1.36 (t, 3H), 3.19 (t, 4H), 3.81 (t, 4H), 4.34 (m, 2H), 7.22 (d, 1H), 7.72 (d, 1H), 7.76 (s, 1H).

A mixture of ethyl 3-morpholino-5-trifluoromethylbenzoate (0.67 g), 1N aqueous sodium hydroxide solution (3.3 ml) and ethanol (6 ml) was stirred and heated to reflux for 15 minutes and then left to stand for 16 hours. The ethanol was evaporated and the residue was dissolved in water (6 ml). Hydrochloric acid (1 M, 3.3 ml) was added and the resultant solid was isolated, washed with water and dried. There was thus obtained 3-morpholino-5-trifluoromethylbenzoic acid as a solid (0.464 g); NMR Spectrum: ($DMSOd_6$) 3.25 (t, 4H), 3.73 (t, 4H), 7.4 (s, 1H), 7.53 (s, 1H), 7.65 (s, 1H), 13.3 (s, 1H).

A solution of 3-morpholino-5-trifluoromethylbenzoyl chloride (11.43 g; obtained by the reaction of the benzoic acid with oxalyl chloride using a conventional procedure) in methylene chloride (200 ml) was added to a stirred mixture of 4-methyl-3-nitroaniline (5.47 g), triethylamine (10 ml) and methylene chloride (200 ml). The resultant mixture was stirred at ambient temperature for 18 hours. The reaction mixture was washed with water and with a saturated aqueous sodium bicarbonate solution, dried ($MgSO_4$) and evaporated. The resultant solid was stirred with diethyl ether (300 ml) for 16 hours. The resultant solid was collected, washed with diethyl ether and dried. There was thus obtained N-(4-methyl-3-nitrophenyl)-3-morpholino-5-fluorobenzamide as a solid (10.4 g); NMR Spectrum: ($CDCl_3$) 2.58 (s, 3H), 3.22 (t, 4H), 3.83 (t, 4H), 7.21 (s, 2H), 7.32 (d, 1H), 7.41 (s, 1H), 7.58 (s, 1H),7.82 (m, 1H), 8.02 (s, 1H), 8.23 (d, 1H).

The compound so obtained was dissolved in ethyl acetate (500 ml) and hydrogenated over 10% palladium-on-carbon catalyst (1.1 g) under 3 atmospheres pressure of hydrogen until the uptake of hydrogen ceased. The catalyst was removed by filtration and the filtrate was evaporated. The residue was triturated under ethyl acetate to give the required starting material (8.1 g); NMR Spectrum: ($CDCl_3$) 2.01 (s, 3H), 3.23 (t, 4H), 3.75 (t, 4H), 4.81 (s, 2H), 6.77 (m, 1H), 6.83 (d, 1H), 7.02 (d, 1H), 7.25 (s, 1H), 7.58 (s, 1H), 7.63 (s, 1H), 9.9 (s, 1H).

Example 77

Pharmaceutical compositions

The following illustrate representative pharmaceutical dosage forms of the invention as defined herein (the active ingredient being termed "Compound X"), for therapeutic or prophylactic use in humans:

(a) Tablet I

Tablet I	mg/tablet
Compound X	100
Lactose Ph.Eur	182.75
Croscarmellose sodium	12.0
Maize starch paste (5% w/v paste)	2.25
Magnesium stearate	3.0

(b) Tablet II

Tablet II	mg/tablet
Compound X	50
Lactose Ph.Eur	223.75
Croscarmellose sodium	6.0
Maize starch	15.0
Polyvinylpyrrolidone (5% w/v paste)	2.25
Magnesium stearate	3.0

(c) Tablet III

Tablet III	mg/tablet
Compound X	1.0
Lactose Ph.Eur	93.25
Croscarmellose sodium	4.0
Maize starch paste (5% w/v paste)	0.75
Magnesium stearate	1.0

(d) Capsule

	mg/capsule
Compound X	10
Lactose Ph.Eur	488.5
Magnesium	1.5

(e) Injection I

	(50 mg/ml)
Compound X	5.0% w/v
1M Sodium hydroxide solution	15.0% v/v
0.1M Hydrochloric acid (to adjust pH to 7.6)	
Polyethylene glycol 400	4.5% w/v
Water for injection to 100%	

(f) Injection II

	(10 mg/ml)
Compound X	1.0% w/v
Sodium phosphate BP	3.6% w/v
0.1M Sodium hydroxide solution	15.0% v/v
Water for injection to 100%	

(g) Injection III

	(1mg/ml, buffered to pH6)
Compound X	0.1% w/v
Sodium phosphate BP	2.26% w/v
Citric acid	0.38% w/v
Polyethylene glycol 400	3.5% w/v
Water for injection to 100%	

(h) Aerosol I

	mg/ml
Compound X	10.0
Sorbitan trioleate	13.5
Trichlorofluoromethane	910.0
Dichlorodifluoromethane	490.0

(i) Aerosol II

	mg/ml
Compound X	0.2
Sorbitan trioleate	0.27
Trichlorofluoromethane	70.0
Dichlorodifluoromethane	280.0
Dichlorotetrafluoroethane	1094.0

(j) Aerosol III

	mg/ml
Compound X	2.5
Sorbitan trioleate	3.38
Trichlorofluoromethane	67.5
Dichlorodifluoromethane	1086.0
Dichlorotetrafluoroethane	191.6

(k) Aerosol IV

	mg/ml
Compound X	2.5
Soya lecithin	2.7
Trichlorofluoromethane	67.5
Dichlorodifluoromethane	1086.0
Dichlorotetrafluoroethane	191.6

(l) Ointment

	ml
Compound X	40 mg
Ethanol	300 µl
Water	300 µl
1-Dodecylazacycloheptan-2-one	50 µl
Propylene glycol	to 1 ml

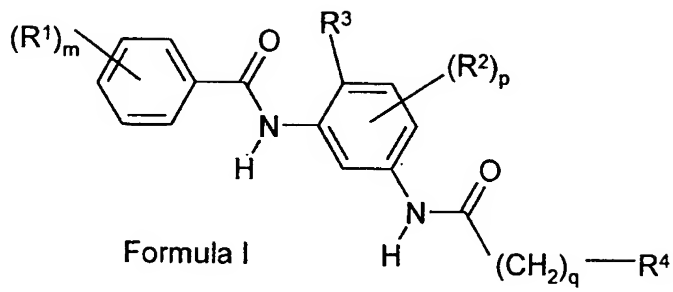
<u>Note</u>

The above formulations may be obtained by conventional procedures well known in the pharmaceutical art. The tablets (a)-(c) may be enteric coated by conventional means, for

example to provide a coating of cellulose acetate phthalate. The aerosol formulations (h)-(k) may be used in conjunction with standard, metered dose aerosol dispensers, and the suspending agents sorbitan trioleate and soya lecithin may be replaced by an alternative suspending agent such as sorbitan monooleate, sorbitan sesquioleate, polysorbate 80, polyglycerol oleate or oleic acid.

CLAIMS

1. A compound of the Formula I



Formula I

wherein R^3 is (1-6C)alkyl or halogeno;

R^1 is selected from the substituents defined in paragraphs (A) and (B) hereinafter:-

(A) hydroxy, halogeno, trifluoromethyl, cyano, mercapto, nitro, amino, carboxy, carbamoyl, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (1-6C)alkanoyl, cyano-(1-6C)alkyl, hydroxy-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkanoyloxy, (1-6C)alkanoylamino, (1-6C)alkoxycarbonylamino, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, aryl, aryl-(1-6C)alkyl, aryl-(1-6C)alkoxy, arylthio, arylsulphinyl, arylsulphonyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl and heterocyclyl-(1-6C)alkyl; and

(B) (1-3C)alkylenedioxy, halogeno-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, carboxy-(1-6C)alkyl, (1-6C)alkoxycarbonyl-(1-6C)alkyl, carbamoyl-(1-6C)alkyl, N-(1-6C)alkylcarbamoyl-(1-6C)alkyl, N,N-di-[(1-6C)alkyl]carbamoyl-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl, hydroxy-(2-6C)alkoxy-(1-6C)alkyl, (1-6C)alkoxy-(2-6C)alkoxy-(1-6C)alkyl, hydroxy-(2-6C)alkylamino-(1-6C)alkyl, (1-6C)alkoxy-(2-6C)alkylamino-(1-6C)alkyl, amino-(2-6C)alkylamino-(1-6C)alkyl, (1-6C)alkylamino-(2-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(2-6C)alkylamino-(1-6C)alkyl, (1-6C)alkylthio-(1-6C)alkyl, hydroxy-(2-6C)alkylthio-(1-6C)alkyl, (1-6C)alkoxy-(2-6C)alkylthio-(1-6C)alkyl, hydroxy-N-(1-6C)alkyl-(2-6C)alkylamino-(1-6C)alkyl, (1-6C)alkoxy-N-(1-6C)alkyl-(2-6C)alkylamino-(1-6C)alkyl,

amino-N-(1-6C)alkyl-(2-6C)alkylamino-(1-6C)alkyl, (1-6C)alkylamino-N-(1-6C)alkyl-(2-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-N-(1-6C)alkyl-(2-6C)alkylamino-(1-6C)alkyl, trifluoromethoxy, halogeno-(2-6C)alkoxy, hydroxy-(2-6C)alkoxy, (1-6C)alkoxy-(2-6C)alkoxy, cyano-(1-6C)alkoxy, carboxy-(1-6C)alkoxy, (1-6C)alkoxycarbonyl-(1-6C)alkoxy, carbamoyl-(1-6C)alkoxy, N-(1-6C)alkylcarbamoyl-(1-6C)alkoxy, N,N-di-[(1-6C)alkyl]carbamoyl-(1-6C)alkoxy, amino-(2-6C)alkoxy, (1-6C)alkylamino-(2-6C)alkoxy, di-[(1-6C)alkyl]amino-(2-6C)alkoxy, halogeno-(2-6C)alkylamino, hydroxy-(2-6C)alkylamino, (1-6C)alkoxy-(2-6C)alkylamino, cyano-(1-6C)alkylamino, carboxy-(1-6C)alkylamino, (1-6C)alkoxycarbonyl-(1-6C)alkylamino, carbamoyl-(1-6C)alkylamino, N-(1-6C)alkylcarbamoyl-(1-6C)alkylamino, N,N-di-[(1-6C)alkyl]carbamoyl-(1-6C)alkylamino, amino-(2-6C)alkylamino, (1-6C)alkylamino-(2-6C)alkylamino, di-[(1-6C)alkyl]amino-(2-6C)alkylamino, N-(1-6C)alkyl-halogeno-(1-6C)alkylamino, N-(1-6C)alkyl-hydroxy-(2-6C)alkylamino, N-(1-6C)alkyl-(1-6C)alkoxy-(2-6C)alkylamino, N-(1-6C)alkyl-cyano-(1-6C)alkylamino, N-(1-6C)alkyl-carboxy-(1-6C)alkylamino, N-(1-6C)alkyl-(1-6C)alkoxycarbonyl-(1-6C)alkylamino, N-(1-6C)alkyl-carbamoyl-(1-6C)alkylamino, N-(1-6C)alkyl-N-(1-6C)alkylcarbamoyl-(1-6C)alkylamino, N-(1-6C)alkyl-N,N-di-[(1-6C)alkyl]carbamoyl-(1-6C)alkylamino, N-(1-6C)alkyl-amino-(2-6C)alkylamino, N-(1-6C)alkyl-(1-6C)alkylamino-(2-6C)alkylamino, N-(1-6C)alkyl-di-[(1-6C)alkyl]amino-(2-6C)alkylamino, (1-6C)alkanesulphonylamino, N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, halogeno-(2-6C)alkanoylamino, hydroxy-(2-6C)alkanoylamino, (1-6C)alkoxy-(2-6C)alkanoylamino, cyano-(2-6C)alkanoylamino, carboxy-(2-6C)alkanoylamino, (1-6C)alkoxycarbonyl-(2-6C)alkanoylamino, carbamoyl-(2-6C)alkanoylamino, N-(1-6C)alkylcarbamoyl-(2-6C)alkanoylamino, N,N-di-[(1-6C)alkyl]carbamoyl-(2-6C)alkanoylamino, amino-(2-6C)alkanoylamino, (1-6C)alkylamino-(2-6C)alkanoylamino, di-[(1-6C)alkyl]amino-(2-6C)alkanoylamino, aryloxy, arylamino, aryl-(1-6C)alkylamino, N-(1-6C)alkyl-aryl-(1-6C)alkylamino, aroylamino, arylsulphonylamino, N-arylsulphamoyl, aryl-(2-6C)alkanoylamino, aryl-(1-6C)alkoxy-(1-6C)alkyl, aryl-(1-6C)alkylamino-(1-6C)alkyl, N-(1-6C)alkyl-aryl-(1-6C)alkylamino-(1-6C)alkyl, heteroaryloxy, heteroaryl-(1-6C)alkoxy, heteroarylamino, heteroaryl-(1-6C)alkylamino, N-(1-6C)alkyl-heteroaryl-(1-6C)alkylamino, heteroarylcarbonylamino, heteroarylsulphonylamino,

N-heteroarylsulphamoyl, heteroaryl-(2-6C)alkanoylamino, heteroaryl-(1-6C)alkoxy-(1-6C)alkyl, heteroaryl-(1-6C)alkylamino-(1-6C)alkyl, N-(1-6C)alkyl-heteroaryl-(1-6C)alkylamino-(1-6C)alkyl, heterocyclyloxy, heterocyclyl-(1-6C)alkoxy, heterocyclylamino, heterocyclyl-(1-6C)alkylamino, N-(1-6C)alkyl-heterocyclyl-(1-6C)alkylamino, heterocyclylcarbonylamino, heterocyclylsulphonylamino, N-heterocyclylsulphamoyl, heterocyclyl-(2-6C)alkanoylamino, heterocyclyl-(1-6C)alkoxy-(1-6C)alkyl, heterocyclyl-(1-6C)alkylamino-(1-6C)alkyl and N-(1-6C)alkyl-heterocyclyl-(1-6C)alkylamino-(1-6C)alkyl;

and wherein any aryl, heteroaryl or heterocyclyl group in a R^1 substituent may optionally bear 1 or 2 substituents selected from halogeno, (1-6C)alkyl and (1-6C)alkoxy;

and wherein any of the substituents defined in paragraph (B) hereinbefore which comprise a CH_2 group which is attached to 2 carbon atoms or a CH_3 group which is attached to a carbon atom may optionally bear on each said CH_2 or CH_3 group a substituent selected from hydroxy, amino, (1-6C)alkoxy, (1-6C)alkylamino and di-[(1-6C)alkyl]amino;

m is 1, 2 or 3;

R^2 is hydroxy, halogeno, trifluoromethyl, cyano, mercapto, nitro, amino, carboxy, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkoxy, (1-6C)alkylamino or di-[(1-6C)alkyl]amino;

p is 0, 1 or 2;

q is 0, 1, 2, 3 or 4; and

R^4 is aryl or cycloalkyl wherein R^4 is substituted with 1, 2 or 3 substituents selected from paragraphs (C) and (D) hereinafter:

(C) hydrogen, hydroxy, halogeno, trifluoromethyl, cyano, mercapto, nitro, amino, carboxy, carbamoyl, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, (1-6C)alkoxycarbonyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (1-6C)alkanoyl, cyano-(1-6C)alkyl, hydroxy-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkanoyloxy, (1-6C)alkanoylamino, (1-6C)alkoxycarbonylamino, N-(1-6C)alkylsulphamoyl, N,N-di-[(1-6C)alkyl]sulphamoyl, aryl, aryl-(1-6C)alkyl, aryl-(1-6C)alkoxy, arylthio, arylsulphinyl, arylsulphonyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl and heterocyclyl-(1-6C)alkyl; and

(D) (1-3C)alkylenedioxy, halogeno-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, carboxy-(1-6C)alkyl, (1-6C)alkoxycarbonyl-(1-6C)alkyl, carbamoyl-(1-6C)alkyl, N-(1-6C)alkylcarbamoyl-(1-6C)alkyl, N,N-di-[(1-6C)alkyl]carbamoyl-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl, hydroxy-(2-6C)alkoxy-(1-6C)alkyl, (1-6C)alkoxy-(2-6C)alkoxy-(1-6C)alkyl, hydroxy-(2-6C)alkylamino-(1-6C)alkyl, (1-6C)alkoxy-(2-6C)alkylamino-(1-6C)alkyl, amino-(2-6C)alkylamino-(1-6C)alkyl, (1-6C)alkylamino-(2-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(2-6C)alkylamino-(1-6C)alkyl, (1-6C)alkylthio-(1-6C)alkyl, hydroxy-(2-6C)alkylthio-(1-6C)alkyl, (1-6C)alkoxy-(2-6C)alkylthio-(1-6C)alkyl, hydroxy-N-(1-6C)alkyl-(2-6C)alkylamino-(1-6C)alkyl, (1-6C)alkoxy-N-(1-6C)alkyl-(2-6C)alkylamino-(1-6C)alkyl, amino-N-(1-6C)alkyl-(2-6C)alkylamino-(1-6C)alkyl, (1-6C)alkylamino-N-(1-6C)alkyl-(2-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-N-(1-6C)alkyl-(2-6C)alkylamino-(1-6C)alkyl, trifluoromethoxy, halogeno-(2-6C)alkoxy, hydroxy-(2-6C)alkoxy, (1-6C)alkoxy-(2-6C)alkoxy, cyano-(1-6C)alkoxy, carboxy-(1-6C)alkoxy, (1-6C)alkoxycarbonyl-(1-6C)alkoxy, carbamoyl-(1-6C)alkoxy, N-(1-6C)alkylcarbamoyl-(1-6C)alkoxy, N,N-di-[(1-6C)alkyl]carbamoyl-(1-6C)alkoxy, amino-(2-6C)alkoxy, (1-6C)alkylamino-(2-6C)alkoxy, di-[(1-6C)alkyl]amino-(2-6C)alkoxy, halogeno-(2-6C)alkylamino, hydroxy-(2-6C)alkylamino, (1-6C)alkoxy-(2-6C)alkylamino, cyano-(1-6C)alkylamino, carboxy-(1-6C)alkylamino, (1-6C)alkoxycarbonyl-(1-6C)alkylamino, carbamoyl-(1-6C)alkylamino, N-(1-6C)alkylcarbamoyl-(1-6C)alkylamino, N,N-di-[(1-6C)alkyl]carbamoyl-(1-6C)alkylamino, amino-(2-6C)alkylamino, (1-6C)alkylamino-(2-6C)alkylamino, di-[(1-6C)alkyl]amino-(2-6C)alkylamino, N-(1-6C)alkyl-halogeno-(1-6C)alkylamino, N-(1-6C)alkyl-hydroxy-(2-6C)alkylamino, N-(1-6C)alkyl-(1-6C)alkoxy-(2-6C)alkylamino, N-(1-6C)alkyl-cyano-(1-6C)alkylamino, N-(1-6C)alkyl-carboxy-(1-6C)alkylamino, N-(1-6C)alkyl-(1-6C)alkoxycarbonyl-(1-6C)alkylamino, N-(1-6C)alkyl-carbamoyl-(1-6C)alkylamino, N-(1-6C)alkyl-N-(1-6C)alkylcarbamoyl-(1-6C)alkylamino, N-(1-6C)alkyl-N,N-di-[(1-6C)alkyl]carbamoyl-(1-6C)alkylamino, N-(1-6C)alkyl-amino-(2-6C)alkylamino, N-(1-6C)alkyl-(1-6C)alkylamino-(2-6C)alkylamino, N-(1-6C)alkyl-di-[(1-6C)alkyl]amino-(2-6C)alkylamino, (1-6C)alkanesulphonylamino, N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, halogeno-(2-6C)alkanoylamino, hydroxy-(2-6C)alkanoylamino, (1-6C)alkoxy-(2-6C)alkanoylamino,

cyano-(2-6C)alkanoylamino, carboxy-(2-6C)alkanoylamino, (1-6C)alkoxycarbonyl-(2-6C)alkanoylamino, carbamoyl-(2-6C)alkanoylamino, N-(1-6C)alkylcarbamoyl-(2-6C)alkanoylamino, N,N-di-[(1-6C)alkyl]carbamoyl-(2-6C)alkanoylamino, amino-(2-6C)alkanoylamino, (1-6C)alkylamino-(2-6C)alkanoylamino, di-[(1-6C)alkyl]amino-(2-6C)alkanoylamino, aryloxy, arylamino, aryl-(1-6C)alkylamino, N-(1-6C)alkyl-aryl-(1-6C)alkylamino, aroylamino, arylsulphonylamino, N-arylsulphamoyl, aryl-(2-6C)alkanoylamino, aryl-(1-6C)alkoxy-(1-6C)alkyl, aryl-(1-6C)alkylamino-(1-6C)alkyl, N-(1-6C)alkyl-aryl-(1-6C)alkylamino-(1-6C)alkyl, heteroaryloxy, heteroaryl-(1-6C)alkoxy, heteroarylamino, heteroaryl-(1-6C)alkylamino, N-(1-6C)alkyl-heteroaryl-(1-6C)alkylamino, heteroarylcarbonylamino, heteroarylsulphonylamino, N-heteroarylsulphamoyl, heteroaryl-(2-6C)alkanoylamino, heteroaryl-(1-6C)alkoxy-(1-6C)alkyl, heteroaryl-(1-6C)alkylamino-(1-6C)alkyl, N-(1-6C)alkyl-heteroaryl-(1-6C)alkylamino-(1-6C)alkyl, heterocyclyloxy, heterocyclyl-(1-6C)alkoxy, heterocyclylamino, heterocyclyl-(1-6C)alkylamino, N-(1-6C)alkyl-heterocyclyl-(1-6C)alkylamino, heterocyclylcarbonylamino, heterocyclylsulphonylamino, N-heterocyclylsulphamoyl, heterocyclyl-(2-6C)alkanoylamino, heterocyclyl-(1-6C)alkoxy-(1-6C)alkyl, heterocyclyl-(1-6C)alkylamino-(1-6C)alkyl and N-(1-6C)alkyl-heterocyclyl-(1-6C)alkylamino-(1-6C)alkyl;

and wherein any aryl, heteroaryl or heterocyclyl group in a substituent on R^4 may optionally bear 1 or 2 substituents selected from halogeno, (1-6C)alkyl and (1-6C)alkoxy;

and wherein any of the substituents defined in paragraph (D) hereinbefore which comprise a CH_2 group which is attached to 2 carbon atoms or a CH_3 group which is attached to a carbon atom may optionally bear on each said CH_2 or CH_3 group a substituent selected from hydroxy, amino, (1-6C)alkoxy, (1-6C)alkylamino and di-[(1-6C)alkyl]amino;

or a pharmaceutically-acceptable salt or in-vivo-cleavable ester thereof;

provided that a substituent on R^4 is selected from paragraph (C) hereinbefore only if at least one R^1 group is selected from paragraph (B) hereinbefore;

and provided that the compounds N-[5-(3-cyclohexylpropionamido)-2-methylphenyl]-3,4-methylenedioxybenzamide and N-{5-[2-(2,3-epoxypropoxy)benzamido]-2-methylphenyl}-2-(2,3-epoxypropoxy)benzamide are excluded.

2. An amide derivative of the Formula I according to claim 1 wherein R^3 is methyl, ethyl, chloro or bromo;

R^1 is selected from the substituents defined in paragraphs (A) and (B) hereinafter:-

(A) hydroxy, fluoro, chloro, trifluoromethyl, cyano, methyl, ethyl, methoxy and ethoxy; and

(B) chloromethyl, methoxymethyl, methylaminomethyl, ethylaminomethyl, dimethylaminomethyl, diethylaminomethyl, 2-hydroxyethylaminomethyl, 2-methoxyethylaminomethyl, 2-chloroethoxy, 3-chloropropoxy, 2-hydroxyethoxy, 3-hydroxypropoxy, 2-methoxyethoxy, 2-ethoxyethoxy, 3-methoxypropoxy, 3-ethoxypropoxy, cyanomethoxy, carboxymethoxy, 2-carboxyethoxy, methoxycarbonylmethoxy, ethoxycarbonylmethoxy, tert-butoxycarbonylmethoxy, 2-methoxycarbonylethoxy, 2-ethoxycarbonylethoxy, 2-tert-butoxycarbonylethoxy, 2-aminoethoxy, 3-aminopropoxy, 2-methylaminoethoxy, 2-ethylaminoethoxy, 3-methylaminopropoxy, 3-ethylaminopropoxy, 2-dimethylaminoethoxy, 2-diethylaminoethoxy, 3-dimethylaminopropoxy, 3-diethylaminopropoxy, 2-pyridylmethoxy, 2-(imidazol-1-yl)ethoxy, 3-(imidazol-1-yl)propoxy, piperidin-4-yloxy, 1-methylpiperidin-4-yloxy, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 2-(4-methylpiperazin-1-yl)ethoxy and 3-(4-methylpiperazin-1-yl)propoxy;

m is 1 or 2;

p is 0;

q is 0; and

R^4 is phenyl wherein R^4 is substituted with 1 or 2 substituents selected from paragraphs (C) and (D) hereinafter:-

(C) hydroxy, fluoro, chloro, trifluoromethyl, cyano, methyl, ethyl, methoxy, ethoxy, methylamino, ethylamino, dimethylamino, diethylamino, phenyl, benzyl, benzyloxy, pyrrolidin-1-yl, piperidino, morpholino, piperazin-1-yl and 4-methylpiperazin-1-yl; and

(D) chloromethyl, methoxymethyl, 2-methoxyethyl, methylaminomethyl, ethylaminomethyl, dimethylaminomethyl, diethylaminomethyl, 2-hydroxyethylaminomethyl, 2-methoxyethylaminomethyl, 2-chloroethoxy, 3-chloropropoxy, 2-hydroxyethoxy,

3-hydroxypropoxy, 2-methoxyethoxy, 2-ethoxyethoxy, 3-methoxypropoxy, 3-ethoxypropoxy, cyanomethoxy, carboxymethoxy, 2-carboxyethoxy, methoxycarbonylmethoxy, ethoxycarbonylmethoxy, tert-butoxycarbonylmethoxy, 2-methoxycarbonylethoxy, 2-ethoxycarbonylethoxy, 2-tert-butoxycarbonylethoxy, 2-aminoethoxy, 3-aminopropoxy, 2-methylaminoethoxy, 2-ethylaminoethoxy, 3-methylaminopropoxy, 3-ethylaminopropoxy, 2-dimethylaminoethoxy, 2-diethylaminoethoxy, 3-dimethylaminopropoxy, 3-diethylaminopropoxy, 2-chloroethylamino, 2-hydroxyethylamino, 2-methoxyethylamino, 2-ethoxyethylamino, 2-aminoethylamino, 2-methylaminoethylamino, 2-ethylaminoethylamino, 2-dimethylaminoethylamino, 2-diethylaminoethylamino, N-(2-chloroethyl)-N-methylamino, N-(2-hydroxyethyl)-N-methylamino, N-(2-methoxyethyl)-N-methylamino, N-(2-ethoxyethyl)-N-methylamino, N-(2-aminoethyl)-N-methylamino, N-(2-methylaminoethyl)-N-methylamino, N-(2-dimethylaminoethyl)-N-methylamino, N-(3-aminopropyl)-N-methylamino, N-(3-methylaminopropyl)-N-methylamino, N-(3-ethylaminopropyl)-N-methylamino, N-(3-dimethylaminopropyl)-N-methylamino, N-(3-diethylaminopropyl)-N-methylamino, 2-pyridylmethoxy, 2-(imidazol-1-yl)ethoxy, 3-(imidazol-1-yl)propoxy, piperidin-4-yloxy, 1-methylpiperidin-4-yloxy, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 2-(4-methylpiperazin-1-yl)ethoxy and 3-(4-methylpiperazin-1-yl)propoxy;
provided that a substituent on R^4 is selected from paragraph (C) immediately above only if at least one R^1 group is selected from paragraph (B) within the R^1 definition immediately above; or a pharmaceutically-acceptable salt thereof.

3. An amide derivative of the Formula I according to claim 1 wherein m is 1, the R^1 group is selected from the substituents defined in paragraph (B) hereinafter and the R^1 group is located at the 3- or 4-position,
or m is 2, at least one R^1 group is selected from the substituents defined in paragraph (B) hereinafter and one R^1 group may be selected from the substituents defined in paragraph (A) hereinafter and the R^1 groups, which may be the same or different, are located at the 3- and 4-positions :-

(A) hydroxy, fluoro, chloro, trifluoromethyl, cyano, amino, methyl, ethyl,

methoxy, ethoxy, methylamino, ethylamino, dimethylamino, diethylamino, aminomethyl, 2-aminoethyl, pyrrolidin-1-yl, piperidino, morpholino, piperazin-1-yl, 4-methylpiperazin-1-yl, pyrrolidin-1-ylmethyl, piperidinomethyl, morpholinomethyl, piperazin-1-ylmethyl and 4-methylpiperazin-1-ylmethyl; and

(B) methylaminomethyl, ethylaminomethyl, dimethylaminomethyl, diethylaminomethyl, 2-hydroxyethylaminomethyl, 2-methoxyethylaminomethyl, 2-aminoethoxy, 3-aminopropoxy, 2-methylaminoethoxy, 2-ethylaminoethoxy, 3-methylaminopropoxy, 3-ethylaminopropoxy, 2-dimethylaminoethoxy, 2-diethylaminoethoxy, 3-dimethylaminopropoxy, 3-diethylaminopropoxy, 2-pyridylmethoxy, 2-(imidazol-1-yl)ethoxy, 3-(imidazol-1-yl)propoxy, piperidin-4-yloxy, 1-methylpiperidin-4-yloxy, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 2-(4-methylpiperazin-1-yl)ethoxy and 3-(4-methylpiperazin-1-yl)propoxy;

p is 0;

R^3 is methyl;

q is 0; and

R^4 is phenyl which is substituted with 1 substituent selected from those defined in paragraph (D) hereinafter and located at the 3- or 4-position,

or R^4 is phenyl which is substituted with 2 substituents, at least one selected from the substituents defined in paragraph (D) hereinafter and one optionally selected from the substituents defined in paragraph (C) hereinafter and the substituents, which may be the same or different, are located at the 3- and 4-positions :-

(C) hydroxy, fluoro, chloro, trifluoromethyl, cyano, amino, methyl, ethyl, methoxy, ethoxy, methylamino, ethylamino, dimethylamino, diethylamino, aminomethyl, 2-aminoethyl, pyrrolidin-1-yl, piperidino, morpholino, piperazin-1-yl, 4-methylpiperazin-1-yl, pyrrolidin-1-ylmethyl, piperidinomethyl, morpholinomethyl, piperazin-1-ylmethyl and 4-methylpiperazin-1-ylmethyl; and

(D) methylaminomethyl, ethylaminomethyl, dimethylaminomethyl, diethylaminomethyl, 2-hydroxyethylaminomethyl, 2-methoxyethylaminomethyl, 2-aminoethoxy, 3-aminopropoxy, 2-methylaminoethoxy, 2-ethylaminoethoxy,

3-methylaminopropoxy, 3-ethylaminopropoxy, 2-dimethylaminoethoxy, 2-diethylaminoethoxy, 3-dimethylaminopropoxy, 3-diethylaminopropoxy, 2-pyridylmethoxy, 2-(imidazol-1-yl)ethoxy, 3-(imidazol-1-yl)propoxy, piperidin-4-yloxy, 1-methylpiperidin-4-yloxy, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 2-(4-methylpiperazin-1-yl)ethoxy and 3-(4-methylpiperazin-1-yl)propoxy;

or a pharmaceutically-acceptable salt thereof;

provided that a substituent on R^4 is selected from paragraph (C) hereinbefore only if at least one R^1 group is selected from paragraph (B) hereinbefore.

4. An amide derivative of the Formula I according to claim 1 wherein m is 1, the R^1 group is selected from the substituents defined in paragraph (B) hereinafter and the R^1 group is located at the 3- or 4-position,

or m is 2 or 3, at least one R^1 group is selected from the substituents defined in paragraph (B) hereinafter and is located at the 3- or 4-position and the other R^1 groups, which may be the same or different, are selected from the substituents defined in paragraphs (A) or (B) hereinafter :-

(A) hydroxy, fluoro, chloro, trifluoromethyl, cyano, amino, methyl, ethyl, methoxy, ethoxy, methylamino, ethylamino, dimethylamino, diethylamino, aminomethyl, 2-aminoethyl, pyrrolidin-1-yl, piperidino, morpholino, piperazin-1-yl, 4-methylpiperazin-1-yl, pyrrolidin-1-ylmethyl, piperidinomethyl, morpholinomethyl, piperazin-1-ylmethyl and 4-methylpiperazin-1-ylmethyl; and

(B) methylaminomethyl, ethylaminomethyl, dimethylaminomethyl, diethylaminomethyl, 2-hydroxyethylaminomethyl, 2-methoxyethylaminomethyl, 2-aminoethoxy, 3-aminopropoxy, 2-methylaminoethoxy, 2-ethylaminoethoxy, 3-methylaminopropoxy, 3-ethylaminopropoxy, 2-dimethylaminoethoxy, 2-diethylaminoethoxy, 2-diisopropylaminoethoxy, 3-dimethylaminopropoxy, 3-diethylaminopropoxy, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 2-(N-methylpyrrolidin-2-yl)ethoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-

ylpropoxy, 2-(4-methylpiperazin-1-yl)ethoxy, 3-(4-methylpiperazin-1-yl)propoxy, 2-pyridylmethoxy, 2-methylthiazol-4-ylmethoxy, 2-(imidazol-1-yl)ethoxy, 3-(imidazol-1-yl)propoxy, piperidin-4-yloxy, N-methylpiperidin-4-yloxy, N-methylhomopiperidin-4-yloxy, pyrrolidin-3-yloxy and N-methylpyrrolidin-3-yloxy;

p is 0;

R^3 is methyl;

q is 0; and

R^4 is phenyl which is substituted with 1, 2 or 3 substituents, which may be the same or different, selected from the substituents defined in paragraphs (C1), (C2) or (D) hereinafter provided that one substituent is selected from the substituents defined in paragraphs (C2) or (D) hereinafter and is located at the 3- or 4-position :-

(C1) hydroxy, fluoro, chloro, trifluoromethyl, cyano, methyl, ethyl, methoxy and ethoxy;

(C2) amino, methylamino, ethylamino, dimethylamino, diethylamino, aminomethyl, 2-aminoethyl, pyrrolidin-1-yl, piperidino, morpholino, piperazin-1-yl, homopiperazin-1-yl, 4-methylpiperazin-1-yl, 4-methylhomopiperazin-1-yl, pyrrolidin-1-ylmethyl, piperidinomethyl, morpholinomethyl, piperazin-1-ylmethyl and 4-methylpiperazin-1-ylmethyl; and

(D) methylaminomethyl, ethylaminomethyl, dimethylaminomethyl, diethylaminomethyl, 2-hydroxyethylaminomethyl, 2-methoxyethylaminomethyl, 2-aminoethoxy, 3-aminopropoxy, 2-methylaminoethoxy, 2-ethylaminoethoxy, 3-methylaminopropoxy, 3-ethylaminopropoxy, 2-dimethylaminoethoxy, 2-diethylaminoethoxy, 3-dimethylaminopropoxy, 3-diethylaminopropoxy, 2-pyridylmethoxy, 2-(imidazol-1-yl)ethoxy, 3-(imidazol-1-yl)propoxy, piperidin-4-yloxy, 1-methylpiperidin-4-yloxy, 2-pyrrolidin-1-ylethoxy, 3-pyrrolidin-1-ylpropoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 2-(4-methylpiperazin-1-yl)ethoxy and 3-(4-methylpiperazin-1-yl)propoxy;

or a pharmaceutically-acceptable salt thereof.

5. An amide derivative of the Formula I according to claim 1 wherein m is 1, the R^1 group is selected from the substituents defined in paragraph (B) hereinafter and the R^1 group is located at the 3- or 4-position,

or m is 2, at least one R^1 group is selected from the substituents defined in paragraph (B) hereinafter and is located at the 3- or 4-position and the other R^1 group is selected from the substituents defined in paragraphs (A) or (B) hereinafter :-

(A) hydroxy, methyl, ethyl, methoxy, ethoxy, dimethylamino, diethylamino, pyrrolidin-1-yl, piperidino, morpholino, piperazin-1-yl, 4-methylpiperazin-1-yl, pyrrolidin-1-ylmethyl, piperidinomethyl, morpholinomethyl, piperazin-1-ylmethyl and 4-methylpiperazin-1-ylmethyl; and

(B) dimethylaminomethyl, diethylaminomethyl, 2-dimethylaminoethoxy, 2-diethylaminoethoxy, 2-diisopropylaminoethoxy, 3-dimethylaminopropoxy, 3-diethylaminopropoxy, 2-(pyrrolidin-1-yl)ethoxy, 3-(pyrrolidin-1-yl)propoxy, 2-(N-methylpyrrolidin-2-yl)ethoxy, 2-piperidinoethoxy, 3-piperidinopropoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 2-piperazin-1-ylethoxy, 3-piperazin-1-ylpropoxy, 2-(4-methylpiperazin-1-yl)ethoxy, 3-(4-methylpiperazin-1-yl)propoxy, 2-pyridylmethoxy, 2-methylthiazol-4-ylmethoxy, piperidin-4-yloxy, N-methylpiperidin-4-yloxy, N-methylhomopiperidin-4-yloxy, pyrrolidin-3-yloxy and N-methylpyrrolidin-3-yloxy;

p is 0;

R^3 is methyl;

q is 0; and

R^4 is phenyl which is substituted at the 3-position with a substituent selected from dimethylamino, diethylamino, pyrrolidin-1-yl, piperidino, morpholino, piperazin-1-yl, homopiperazin-1-yl, 4-methylpiperazin-1-yl and 4-methylhomopiperazin-1-yl and is optionally substituted with a further substituent selected from fluoro, chloro, cyano, methyl and trifluoromethyl;

or a pharmaceutically-acceptable salt thereof.

6. An amide derivative of the Formula I according to claim 1 wherein R^3 is methyl;

p is 0;

q is 0;

$(R^1)_m$ is 4-diethylaminomethyl, 3-(2-diethylaminoethoxy), 3-(2-diisopropylaminoethoxy), 3-(3-diethylaminopropoxy), 3-(2-pyrrolidin-1-ylethoxy), 3-[2-(N-methylpyrrolidin-2-yl)ethoxy], 3-(2-piperidinoethoxy), 3-(3-piperidinopropoxy), 4-[3-(4-methylpiperazin-1-yl)propoxy], 4-methoxy-3-(2-pyrrolidin-1-ylethoxy), 4-methoxy-3-(2-piperidinoethoxy), 4-methoxy-3-(3-piperidinopropoxy), 4-methoxy-3-(2-diethylaminoethoxy), 4-methoxy-3-(3-diethylaminopropoxy), 4-methoxy-3-[2-(N-methylpyrrolidin-2-yl)ethoxy], 4-(2-pyridylmethoxy), 4-(2-methylthiazol-4-ylmethoxy), 3-piperidin-4-yloxy, 4-piperidin-4-yloxy, 3-(N-methylhomopiperidin-4-yloxy) and 3-pyrrolidin-3-yloxy; and

R^4 is 3-pyrrolidin-1-ylphenyl, 3-piperidinophenyl, 3-morpholinophenyl, 3-fluoro-5-morpholinophenyl or 3-morpholino-5-trifluoromethylphenyl;

or a pharmaceutically-acceptable salt thereof.

7. A compound of the Formula I according to claim 1 selected from :-

N-{5-[4-(3-hydroxypropoxy)benzamido]-2-methylphenyl}-3,4-dimethoxybenzamide,

N-[5-(3-dimethylaminobenzamido)-2-methylphenyl]-4-(2-methoxyethoxy)benzamide,

N-[5-(4-cyanobenzamido)-2-methylphenyl]-4-(2-methoxyethoxy)benzamide,

N-[2-chloro-5-(4-cyanobenzamido)phenyl]-4-[2-(imidazol-1-yl)ethoxy]benzamide,

N-[2-methyl-5-(3-morpholinobenzamido)phenyl]-3-piperidin-4-yloxybenzamide,

N-[2-methyl-5-(3-morpholinobenzamido)phenyl]-3-(2-pyrrolidin-1-ylethoxy)benzamide,

N-[2-methyl-5-(3-morpholinobenzamido)phenyl]-3-(2-diethylaminoethoxy)benzamide,

N-[2-methyl-5-(3-morpholinobenzamido)phenyl]-4-methoxy-3-(2-pyrrolidin-1-ylethoxy)benzamide,

N-[2-methyl-5-(3-morpholinobenzamido)phenyl]-4-diethylaminomethylbenzamide,

N-[2-methyl-5-(3-morpholinobenzamido)phenyl]-4-[3-(4-methylpiperazin-1-yl)propoxy]benzamide,

N-[2-methyl-5-(3-morpholinobenzamido)phenyl]-3-[2-(N-methylpyrrolidin-2-yl)ethoxy]benzamide,

N-[2-methyl-5-(3-pyrrolidin-1-ylbenzamido)phenyl]-3-piperidin-4-yloxybenzamide,

N-[2-methyl-5-(3-piperidinobenzamido)phenyl]-3-piperidin-4-yloxybenzamide,

N-[2-methyl-5-(3-morpholinobenzamido)phenyl]-3-(N-methylhomopiperidin-

4-yloxy)benzamide,

N-[5-(3-fluoro-5-morpholinobenzamido)-2-methylphenyl]-3-piperidin-4-yloxybenzamide

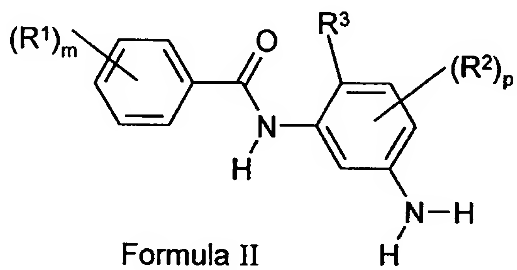
N-[2-methyl-5-(3-morpholinobenzamido)phenyl]-4-(2-pyridylmethoxy)benzamide,

N-[5-(3-fluoro-5-morpholinobenzamido)-2-methylphenyl]-4-diethylaminomethylbenzamide and N-[5-(3-fluoro-5-pyrrolidin-1-ylbenzamido)-2-methylphenyl]-4-diethylaminomethylbenzamide;

or the pharmaceutically-acceptable salts thereof.

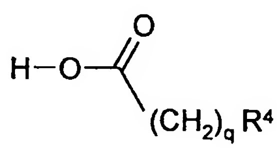
8. A process for the preparation of an amide derivative of the Formula I, or a pharmaceutically-acceptable salt or in-vivo-cleavable ester thereof, according to claim 1 which comprises:-

(a) the reaction of a compound of the Formula II



Formula II

with an acid of the Formula III



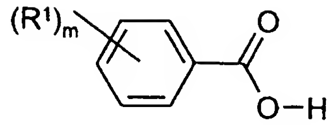
Formula III

or an activated derivative thereof, under standard amide bond forming conditions, wherein variable groups are as defined in claim 1 and wherein any functional group is protected if necessary, and:

(i) removing any protecting groups;

(ii) optionally forming a pharmaceutically-acceptable salt or in-vivo-cleavable ester;

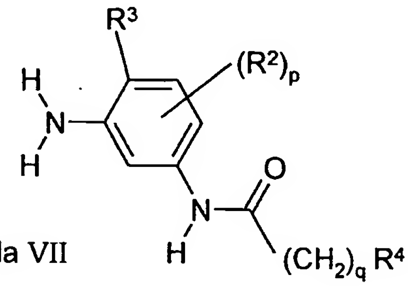
(b) the reaction of an acid of the Formula V



Formula V

or an activated derivative thereof, with an aniline of the Formula VII

Formula VII



under standard amide bond forming conditions, wherein variable groups are as defined in claim 1 and wherein any functional group is protected, if necessary, and:

(i) removing any protecting groups;

(ii) optionally forming a pharmaceutically-acceptable salt or in-vivo-cleavable ester;

(c) for the preparation of a compound of the Formula I according to claim 1 wherein R^1 or a substituent on R^4 is (1-6C)alkoxy or substituted (1-6C)alkoxy, (1-6C)alkylthio, (1-6C)alkylamino, di-[(1-6C)alkyl]amino or substituted (1-6C)alkylamino or heterocyclyloxy, the alkylation, conveniently in the presence of a suitable base, of an amide derivative of the Formula I wherein R^1 or a substituent on R^4 is hydroxy, mercapto or amino as appropriate;

(d) for the preparation of a compound of the Formula I according to claim 1 wherein R^1 or a substituent on R^4 is (1-6C)alkanoylamino or substituted (2-6C)alkanoylamino, the acylation of a compound of the Formula I wherein R^1 or a substituent on R^4 is amino;

(e) for the preparation of a compound of the Formula I according to claim 1 wherein R^1 or a substituent on R^4 is (1-6C)alkanesulphonylamino, the reaction of a compound of the Formula I wherein R^1 or a substituent on R^4 is amino with a (1-6C)alkanesulphonic acid, or an activated derivative thereof;

(f) for the preparation of a compound of the Formula I according to claim 1 wherein R^1 or a substituent on R^4 is carboxy, carboxy-(1-6C)alkyl, carboxy-(1-6C)alkoxy, carboxy-(1-6C)alkylamino, N-(1-6C)alkyl-carboxy-(1-6C)alkylamino or

carboxy-(2-6C)alkanoylamino, the cleavage of a compound of the Formula I wherein R^1 or a substituent on R^4 is (1-6C)alkoxycarbonyl, (1-6C)alkoxycarbonyl-(1-6C)alkyl, (1-6C)alkoxycarbonyl-(1-6C)alkoxy, (1-6C)alkoxycarbonyl-(1-6C)alkylamino, N-(1-6C)alkyl-(1-6C)alkoxycarbonyl-(1-6C)alkylamino or (1-6C)alkoxycarbonyl-(2-6C)alkanoylamino as appropriate;

(g) for the preparation of a compound of the Formula I according to claim 1 wherein R^1 or a substituent on R^4 is amino-(1-6C)alkyl, heterocyclyl-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di-[(1-6C)alkyl]amino-(1-6C)alkyl, substituted (2-6C)alkylamino-(1-6C)alkyl or substituted N-(1-6C)alkyl-(2-6C)alkylamino-(1-6C)alkyl, the reaction of a compound of the Formula I wherein R^1 or a substituent on R^4 is a group of the formula -(1-6C)alkylene-Z wherein Z is a displaceable group with an appropriate amine or heterocyclyl compound;

(h) for the preparation of a compound of the Formula I according to claim 1 wherein R^1 or a substituent on R^4 is amino, heterocyclyl, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, substituted (1-6C)alkylamino, substituted N-(1-6C)alkyl-(1-6C)alkylamino, substituted (2-6C)alkylamino or substituted N-(1-6C)alkyl-(2-6C)alkylamino, the reaction of a compound of the Formula I wherein R^1 or a substituent on R^4 is a displaceable group Z with an appropriate amine or heterocyclyl compound;

(i) for the preparation of a compound of the Formula I according to claim 1 wherein R^1 or a substituent on R^4 is N-(1-6C)alkyl-(1-6C)alkanesulphonylamino, the alkylation, conveniently in the presence of a suitable base, of an amide derivative of the Formula I wherein R^1 or a substituent on R^4 is (1-6C)alkanesulphonylamino;

(j) for the preparation of a compound of the Formula I according to claim 1 wherein R^1 or a substituent on R^4 is a hydroxy-heterocyclyl-(1-6C)alkoxy group, a hydroxy-(1-6C)alkylamino-(2-6C)alkoxy group or a hydroxy-di-[(1-6C)alkyl]amino-(2-6C)alkoxy group, the reaction of a compound of the Formula I wherein R^1 or a substituent on R^4 is a epoxy-substituted (1-6C)alkoxy group with a heterocyclyl compound or an appropriate amine; or

(k) for the preparation of a compound of the Formula I according to claim 1 wherein R^1, R^2 or a substituent on R^4 is an amino group, the reduction of a compound of the Formula I wherein R^1, R^2 or a substituent on R^4 is a nitro group.

9. A pharmaceutical composition which comprises an amide derivative of the Formula I,

or a pharmaceutically-acceptable salt or in-vivo-cleavable ester thereof, according to claim 1 in association with a pharmaceutically-acceptable diluent or carrier.

10. The use of an amide derivative of the Formula I, or a pharmaceutically-acceptable salt or in-vivo-cleavable ester thereof, according to claim 1 in the manufacture of a medicament for use in the treatment of medical conditions mediated by cytokines.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 99/01489

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07C235/56 A61K31/165

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07C A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 99 15164 A (BROWN GEORGE ROBERT ;COHEN PHILIP (GB); ZENECA LTD (GB); BROWN DEA) 1 April 1999 (1999-04-01) claims 1-12	1-10
P,X	WO 98 22103 A (HEDGE PHILIP JOHN ;ZENECA LTD (GB); BOYLE FRANCIS THOMAS (GB)) 28 May 1998 (1998-05-28) claims 1-13	1-10
P,A	EP 0 849 256 A (JAPAN TOBACCO INC) 24 June 1998 (1998-06-24) the whole document	1
A	& WO 97 08133 A (JAPAN TOBACCO INC) 6 March 1997 (1997-03-06) the whole document	1

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 August 1999	09/09/1999

Name and mailing address of the ISA	Authorized officer
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Int. tional Application No
PCT/GB 99/01489

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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A	HANSON G J: "inhibitors of p38 kinase" EXPERT OPINION ON THERAPEUTIC PATENTS, vol. 7, no. 7, 1 January 1997 (1997-01-01), pages 729-733, XP002086152 ISSN: 1354-3776 cited in the application -----	1

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte ional Application No
PCT/GB 99/01489

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		NO 992336 A	14-05-1999
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